

REITER'S DISEASE
A STUDY OF 344 CASES OBSERVED
IN FINLAND

BY
ILMARI PARONEN

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FROM THE 56th WAR HOSPITAL AND THE KIVELÄ HOSPITAL, HELSINKI
DIRECTOR PROFESSOR PAULI SOISALO, M. D.

AND FROM MEDICAL CLINIC II, UNIVERSITY OF HELSINKI
DIRECTOR AT THAT TIME PROFESSOR ÖSTEN HOLSTI, M. D.

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ILMARI PARONEN

TO BE PUBLICLY DISCUSSED, BY PERMISSION OF THE MEDICAL
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PREFACE

Interest was stimulated in this work by a case of Reiter's disease observed by me at a field hospital on the Karelian Isthmus in Autumn 1943. The war gave me excellent opportunities of collecting material, but studying it thoroughly and from different aspects was, of course, more difficult than in normal circumstances. During the course of the investigation foreign literature — particularly English and American — was almost unobtainable. — The historical part of the work may seem too long to the reader, but as a uniform and comprehensive conception of the disease is difficult to obtain from previous studies of the subject, this length seems justified.

It is a great pleasure to thank my former chief and teacher, Professor P. Soisalo, M.D., Director of the Medical Department of the Kivelä Hospital, Helsinki. He helped me by arranging for the collection of the material and personally supervised my work in all its stages, giving me invaluable advice.

My sincere thanks are also due to my former chief and teacher, Professor Östen Holsti, M.D., Head of Medical Clinic III of the University of Helsinki, who has followed the progress of my work with unfailing interest and made valuable suggestions.

I also wish to thank Professor K. O. Renkonen, M.D., Head of the Department of Serology and Bacteriology in the University of Helsinki, who has been helpful in regard to the sero-bacteriological part of this work.

I remember with gratitude all those colleagues, nurses, "Lottas", and others who have in many ways helped me in my work; among them particularly O. Helve, M.D., and A. Korhonen, M.D., Uni-

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Finally I wish to thank Miss Aino Wuolle, Mag. Phil., for translating the work into English.

Helsinki, September, 1947

Ilmari Paronen

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DEFINITION AND NOMENCLATURE

Reiter's disease may be defined as a syndrome of unknown aetiology characterized by three essential symptoms, arthritis, conjunctivitis and urethritis. The syndrome is in most cases, but by no means always, post-dysenteric. The three cardinal symptoms — not always all present — form the framework of the syndrome which can be accompanied by other symptoms from almost any system.

Many names have been used for this disease; the most important are: *Rheumatismus intestinalis cum ulcere* (Cælius Aurelianus), *Arthritis* or *Polyarthritidis dysenterica* (Huette 1869, Korczynski 1874, Schittenhelm and Schlecht 1918, Manson-Bahr 1920, Kielland 1939, etc.), *Arthritis* or *Polyarthritidis enterica* (Schittenhelm and Schlecht 1918, Tiemann 1932, etc.), *Ruhrreumatismus* (Dorendorf 1917, Walther 1940 c, etc.), *Ruhrreumatoid* (Schemensky 1918, Kempf 1944, etc.), *Arthritis* or *Polyarthritidis urethritica* (Moltke 1936, Clemmesen and Kalbak 1938), *Syndrome conjunctivo-urétro-synovial* (Fiessinger and Leroy 1916), *Reiter's disease* (Musger 1934, Beck 1937, Hollander *et al.* 1945, Bergmark 1946, Feiring 1946, Löfgren 1946, Reimann 1946, Twiss and Douglas 1946, Vallee 1946, etc.), and *Spirochaetosis arthritica* (Reiter 1916, 1917, 1921 and 1941, Frühwald 1927).

The names here enumerated are not particularly well-chosen as none of them expresses the essential in the disease, and each of them refers only to one or another of its features. The lack of a suitable name is mainly due to the fact that our knowledge of this syndrome is still in many respects limited.

In the present work the names Reiter's disease or syndrome and dysenteric arthritis are used, chiefly because they seem to be those most frequently employed. The former is to be considered rather inappropriate, as Reiter cannot be regarded as the first or even an important observer of the disease. However, this name is most widely used — in America exclusively — and so seems justified because it facilitates understanding of the concepts. Nor is the name dysenteric arthritis very well-chosen either, although, in a way, it describes the nature of the disease and its relation to dysentery. Thus it seems best to leave the name undecided until our knowledge of the ætiology and pathogenesis of the disease is wider.

HISTORICAL SURVEY

According to Manson-Bahr (1943), articular complications following dysentery were known even to Cælius Aurelianus who lived at the beginning of the fifth century. Huette (1869) states that arthritides after dysentery had already been described by Zimmermann (1765), Lepecq de la Clôture (1765 and 1767), Stoll (1776 and 1777), and Thomas (1835). Cases of post-dysenteric joint disease were published before Reiter's time also by Gauster (1869), Korczynski (1874), Quinquand (1874), Rapmund (1874), and Remlinger (1898, 1901). As regards the other symptoms of the syndrome Stoll (1776—1777) reported dysuria in combination with arthritis and Remlinger (1901) observed acute nephritis in one of his cases besides arthritis. Kräuter (1871) described cases in which polyarthritis as well as conjunctivitis were noted after dysentery, and in Markwald's (1904) case all three symptoms, conjunctivitis, urethritis, and gonitis, appeared. Singer (1915), in addition to his cases of "dysenteric rheumatoid", reported cases of myalgia, neuralgia, conjunctivitis, and urethritis. Post-dysenteric syndromes were described in the same year as Reiter's (1916) case by Cahn, Dorendorf and Kolle, Fiessinger and Leroy, Rist, Crouzon, and Rose. In 1916 Waelsch reported two cases without previous dysentery. One of these had urethritis, prostatitis and polyarthritis, the second urethritis and conjunctivitis. In the recent literature the writer has found over 80 reports dealing with Reiter's syndrome. The most extensive of them are Dorendorf's (1917) report of 59 cases. Schittenhelm and

Schlecht's (1918) of 140 cases, Walther's (1940 c) of 188 cases, Cimbal's (1942) of 114 cases, and Hollander's (1946) of 53.

Reiter's disease seems to have occurred in some measure in all European countries, also in the north, Denmark, Sweden, Norway, and in Finland where Thesleff (1937) has published one case. It has also been noted in India, Africa and America.

Not nearly all the published cases have been post-dysenteric. Perhaps just for this reason several investigators have avoided the adjectives *enterica* and *dysenterica* in naming the disease and published their cases as Morbus or Syndroma Reiter.

The frequency of the syndrome during epidemics of dysentery seems to vary greatly. The lowest and highest incidence figures given are 0.27 and 10 per cent (Dorendorf and Kolle 1916, Schlierbach 1941, Manson-Bahr 1943, etc.). It has also been noted that in one and the same locality the disease has appeared during one epidemic, but not during another, later one (Huette 1869, Manson-Bahr 1943). Further, observations have been made as to the nature of the dysentery later complicated by Reiter's syndrome. According to Dorendorf (1917), the dysentery in itself is then mild, whereas Walther (1941) considers that very mild and very severe cases do not lead to this complication. In Schittenhelm and Schlecht's (1918) series the dysentery and the subsequent polyarthritis were both severe in 20 per cent of the cases, in 32 per cent a mild dysentery was followed by a severe polyarthritis, and in 48 per cent both were mild. In addition there were 34 cases unaccompanied by any noteworthy enteritic symptoms, but as they were concurrent with the other cases, the cause was assumed to be the same. Attempts have also been made to discover what kind of dysentery causes Reiter's disease. In summarizing it may be stated that Reiter's syndrome seems to occur in toxic and non-toxic forms of bacillary dysentery, as it has been observed in Shiga-Kruse's dysentery (Markwald 1904, Cahn 1916, Sick 1918, Schittenhelm and Schlecht 1918, Manson-Bahr 1920 and 1943, Steenis 1931, Walther 1940 a and 1941, Krieger 1940, Cimbal 1942, Beiglböck 1943), in Flexner's dysentery (Kittsteiner 1915, Cahn 1916, Sick 1918, Worms, Lesbire and Sourdille 1927, Walther 1940 a and 1941, Kruspe 1941, Cimbal 1942, Beiglböck

1943, Kokko 1945), and in E-dysentery (Walther 1940 a and 1941). Arthritis complicating amœbic dysentery has also been described (Moorhead 1916, Manson-Bahr 1920).

Some authors consider that Reiter's disease does not occur in women, but only in young adult males (Löfgren 1938 and 1946, Arén and Lindgren 1945, Storm-Mathisen 1945, Twiss and Douglas 1946, Vallee 1946). However, Huette (1869), Gauster (1869), and Rapmund (1874) have noted forms with joint symptoms also in women, while Kräuter (1871) has observed in women the syndrome — conjunctivitis and arthritis — and Schittenhelm (1920) once — arthritis and vaginitis. Lever and Crawford (1944) and Young and McEwen (1947) have also each reported one female case; of Zewi's (1947) ten cases six were female and one a boy of 4.

As regards the order in which the essential symptoms appear it has been observed that any of these — arthritis, conjunctivitis or urethritis alone or in any combination — may initiate the disease. According to the literature, however, the triad does not evolve in nearly all cases, but the disease may also occur with two or even one essential symptom. Yet both ocular and urethral lesions seem to occur relatively seldom alone or together as the only sign of the syndrome. On the contrary, joint lesions appear in several series in the majority of cases as the only symptom, at times even in all cases. The diagnosis has then been based on the fact that the joint disease had appeared following a dysentery, or, if not, cases of dysentery and Reiter's triad had occurred in the environment.

ARTHRITIS

In the clinical picture of Reiter's disease articular affections seem to predominate and are extremely seldom absent. They generally appear after the symptoms of dysentery have subsided, more rarely while they are still present (Huette 1869, Gauster 1869, Kräuter 1871, Quinquand 1874, Schittenhelm and Schlecht 1918, Gantenberg 1939). According to Walther (1940 a and 1941), the joint symptoms may occasionally be observed even during the period of incubation and appear one to

two days before the enteritic symptoms or simultaneously with them. He uses the name "Frühhreumatismus" with reference to these cases as distinct from "Spätrheumatismus" with a later onset. However, the interval between the dysentery and Reiter's disease may even be some months. In one case reported by Zewi (1947) it was two months and Kräuter (1871) observed post-dysenteric arthritic symptoms four months after the disappearance of bloody diarrhoea. In this case, however, the dysentery had been followed by chronic colitis and it is thus possible that the dysentery was of unusually long duration.

According to Dorendorf (1917) and Schittenhelm and Schlecht (1918), the great majority of the cases began within two to four weeks from the onset of dysentery.

In the great majority of cases the arthritis seems to be poly-articular in character. Thus Schittenhelm and Schlecht's series consists of 124 poly- and 12 monarthritides. The different joints become involved at the same time or successively. The joint feels tender on movement and there is spontaneous pain particularly at night. Later, articular swelling and effusion appear and occasionally the affected joint also becomes hot (Gauster 1869, Schittenhelm and Schlecht 1918, Balban 1934, Hollander *et al.* 1945, Jackson 1946, Wrigley 1946, *etc.*) and red (Gauster 1869, Schittenhelm and Schlecht 1918, Balban 1934, Hollander *et al.* 1945, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*). The severity of the effusion seems to vary considerably from case to case and also in the different joints of the same patient. Thus the joints may sometimes be only very slightly swollen, while sometimes — for instance when the knee joint is involved — unbearable pain may be caused by the excessive formation of synovial fluid in the joint cavity (Schittenhelm and Schlecht 1918, Beiglböck 1943, *etc.*). Occasionally the clinical picture may resemble that of gonorrhœal arthritis (Huette 1869, Brugsch 1930, Hollander *et al.* 1945) or of gout (Schittenhelm and Schlecht 1918).

The clinical manifestations described by Dorendorf (1917) differ from the above in that he reports no redness of the affected joints.

According to the literature, there has been a form of the disease in which no evident or recognizable changes in the joints were observed and articular pain was the only symptom (Schittenhelm and Schlecht 1918, *etc.*). Remlinger (1898) distinguishes two main types of articular involvement: the polyarticular type with migratory pain and the hydrarthrodial type, resistant to all therapy. He states that the two forms may appear concurrently in the same patient. Walther (1940 c) similarly divides these articular affections into two groups, "Arthralgia" and "Gelenkrheuma". His series of Reiter's disease includes 64 of the former and 46 of the latter.

Articular suppuration has not occurred, according to the literature. Although Huette (1869) states that earlier researchers have commented on such cases, these suppurating joints can hardly be associated with Reiter's disease and are probably due to secondary infection arising in consequence of aspiration or some other factor, *e.g.* a concurrent suppurative process (*Cf.* p. 80).

According to Remlinger (1898), Schittenhelm and Schlecht (1918), Stühmer (1921), *etc.*, the synovial exudate is yellowish, viscous, only slightly turbid, and fibrinous; it has an albumen content of 1.3—4 per cent (Esbach), contains more fibrin the older it is, and the inflammatory cells are chiefly polymorphonuclears. Vallee (1946), on the other hand, states that the number of lymphocytes practically equals that of the polymorphonuclear cells. Beiglböck (1943) reports that in his series the aspirated fluid contained from 1,000 to 5,000 leucocytes per cu. mm. and Hollander *et al.* (1945) obtained 9,000 to 14,000 leucocytes per cu. mm.; of them 65—70 per cent were neutrophils.

Writers agree in all essentials regarding the frequency of involvement of the different joints. It is thus evident that in the great majority of cases the joints of the lower extremities are more commonly affected than those of the upper, and the large joints much more often than the small joints (Dorendorf 1917, Stettner 1917, Schittenhelm and Schlecht 1918, Cimbal 1942, Beiglböck 1943, Hollander *et al.* 1945). This is illustrated in the table below showing the distribution of joint involvement in Schittenhelm and Schlecht's 136 cases:

Joints involved	No. of cases	Joints involved	No. of cases
Knee	137	Spine	7
Ankle	107	Sternoclavicular	6
Wrist	41	Sacrum	6
Shoulder	33	Temporomandibular	5
Elbow	23	Metacarpal	4
Toe	23	Metatarsal	4
Finger	22	Art. acromioclavicularis	2
Hip	20	Larynx	1

According to Huette (1869) and Dorendorf (1917), the articulations of the right side seem to be affected somewhat more often than those on the left. Dorendorf further reports his observation that the weight-bearing joints are more likely to be involved than those subject to less strain. Yet his series seems to be too small to warrant such a conclusion.

Some investigators hold that the course of the arthritis resembles the migratory type of polyarthritis seen in rheumatic fever (Kräuter 1871, Korczynski 1874, Feiring 1946, Vallee 1946, Pinck 1947). Most observers consider, however, that there is no migration of symptoms from one joint to another.

The duration of arthritis seems to vary considerably from case to case, according to the literature. Thus, in some patients, the joint lesions may disappear within a few days, yet in the majority they last for weeks or months (Huette 1869, Gauster 1869, Stühmer 1921, Twiss and Douglas 1946, *etc.*). In the series of Hollander *et al.* (1945) the duration varied from three to eight months, but in some cases there were symptoms even after eight months. Schittenhelm and Schlecht (1918) state that arthritic symptoms have been observed in a few extremely rare cases for as much as two years. Dorendorf (1917) watched the course of the disease in 12 patients from the onset to the disappearance of symptoms and found that it lasted from 35 days to 12 months, in one case more than one year.

The literature seems to contain comparatively few statements as to the recurrence of arthritis. This may be due to the fact that most investigators have dealt with soldiers on active duty and the patients were mostly transferred during the course of

treatment from hospitals in the theatre of operation to the home area. Consequently, in the vast majority of the cases it has not been possible to follow the course of the disease to the end, and there are no data regarding possible recurrences. According to Quinquand (1874), dysenteric arthritis leaves no predisposition to recurrence; some recent observers, however, have reported recurrence of the joint complications (Cf. p. 32).

Involvements of the bursae, tendons, tendon sheaths and synovial membranes are closely related to the articular symptoms. They may be concurrent with the joint disease or appear independently, the joints remaining unaffected (Dorendorf and Kolle 1916, Dorendorf 1917, Stettner 1917, Schittenhelm and Schlecht 1918, Sick 1918, Stühmer 1921, Paetzel 1928, Raschewskaja 1935, Gantenberg 1939, Walther 1941, Kempf 1944, *etc.*). Schittenhelm and Schlecht's (1918) series contained six cases of tendovaginitis and four of periostitis. On X-ray examination Hollander *et al.* (1945) noted periosteal proliferation in three cases, but radiographs taken later showed that it had disappeared in two of them.

Muscular pain seems also to occur in connection with Reiter's disease (Gauster 1869, Cahn 1916, Rose 1916). This so-called "Muskelrheuma" appeared in 116 of Walther's (1940 c) 188 cases. Schemensky (1918) has noted a persistent "muscular rheumatism" in 2 per cent of his cases during convalescence from dysentery, and Kokko (1945), in his series from Finland, muscular pain in 52 per cent at the acute stage of dysentery. The latter high percentage may, however, include cases in which the pain may be attributed to the same causes as in acute fever in general.

Röntgen studies of the affected joints have shown osteoporosis and slight signs of bone destruction, occasionally also periosteal proliferation (Frühwald 1927, Paetzel 1928, Salvesen 1937, Hollander *et al.* 1945, Feiring 1946, Sjöberg 1946, Twiss and Douglas 1946, Vallee 1946, Pinck 1947). These changes did not appear until two months after the onset (Hollander *et al.* 1945, Twiss and Douglas 1946) and were most pronounced in the small joints where also ankylosis was noted (Paetzel 1928, Twiss and Douglas 1946).

OCULAR LESIONS

According to reports in the literature, eye affections are generally concomitant with the arthritis (Kräuter 1871, Dorendorf and Kolle 1916, Schittenhelm and Schlecht 1918, Manson-Bahr 1920, Walther 1940 c, etc.), but sometimes the former are accompanied by lesions of the urinary tract only (Waelsch 1916, Dorendorf 1917, Stühmer 1921, and Beiglböck 1943), or appear quite alone (Dorendorf 1917, Manson-Bahr 1920, Kokko 1945). Ocular affections may also initiate the disease and the arthritis appear later (Dorendorf 1917, Stettner 1917, Schittenhelm 1920, and Beiglböck 1943). Variable figures of incidence have been reported for the eye affections. Of 610 patients with dysentery recorded by Steenis (1931) twelve developed eye symptoms, of Holler's (1941) 1,620 patients 21, and of Kokko's (1945) 555 patients 111. About one-half of Kokko's patients showed inflammatory changes in the *conjunctiva sclerae*. Two of his patients had a concomitant arthritis and urethritis and several showed the triad — eye pains (or mild conjunctivitis), joint pain, and "burning" on urination. More often still two symptoms appeared together, the most common combination being eyes and joints; that of eyes and urethra was much less frequent, and that of urethra and joints was observed only in a few cases. Dorendorf (1917) reports that conjunctivitis unaccompanied by arthritic or urethritic symptoms occurred as a complication of dysentery in 3 per cent of his cases. He gives the incidence of conjunctivitis in Reiter's disease as 25.5 per cent, whereas 29 per cent is quoted by Schittenhelm (1920), 68 per cent by Gounelle *et al.* (1941), 82 per cent by Cimbali (1942), and 4.5 per cent by Walther (1941).

Conjunctivitis, either bilateral or unilateral, seems to be the most common ocular manifestation. In bilateral cases it may start in both eyes simultaneously or first in one and later in the other eye. The degree of severity varies greatly, from quite mild injection of the conjunctivæ to an intense purulent conjunctivitis which latter may be attended by marked chemosis, œdema of the lids, and a tendency of the lids to stick (Kräuter 1871, Dorendorf 1917, Schittenhelm and Schlecht 1918, Sommer

1918, Stühmer 1921, Walther 1940 c and 1941, Kokko 1945, *etc.*). Besides a redness of the conjunctiva, episcleral hyperæmia has often been noted; to this has been attributed the deep purple colour characteristic of the conjunctivitis seen in Reiter's disease.

Cases of iritis, keratitis, corneal ulceration, and irido-cyclitis have also been described (Reiter 1916, Dorendorf 1917, Stettner 1917, Schittenhelm and Schlecht 1918, Sick 1918, Manson-Bahr 1920, Stühmer 1921, Worms *et al.* 1927, Brugsch 1931, Cimbäl 1942, Haarr 1945, Hollander *et al.* 1945, Tengroth 1945, Bergmark 1946, Feiring 1946, Jackson 1946, Vallee 1946, Wrigley 1946, Zewi 1947). Optic neuritis was noted in two cases by Zewi (1947); in one there was also a conjunctivitis and in the other a kerato-iritis.

On microscopical examination the ocular exudate was found to contain a large number of leucocytes and few epithelial cells, the results of the bacteriological examination being either negative or showing only a few cocci (Schittenhelm and Schlecht 1918, Sommer 1918, Stühmer 1921, Kruspe 1941, Feiring 1946, Twiss and Douglas 1946, *etc.*).

There are only a few statements in the literature regarding the duration of the eye affections, *e.g.* that the conjunctivitis generally lasts for a few days or weeks, rarely longer (Stettner 1917, Schittenhelm and Schlecht 1918, Sommer 1918, Hollander *et al.* 1945, Jackson 1946, Twiss and Douglas 1946). One and a half to four months has been mentioned as the duration of iritis and keratitis (Stühmer 1921, Zewi 1947). Recurrences of the eye affections have also been reported (Kräuter 1871, Stettner 1917, Stühmer 1921, Cimbäl 1942), even years after complete recovery (Vallee 1946, Twiss and Douglas 1946).

UROGENITAL INVOLVEMENT

According to most observers, diseases of the urinary system occupy the third place in the symptom triad. Urethritis is considered the commonest and occurs in Schittenhelms and Schlecht's (1918) series in 6 per cent, in Gounelle's *et al.* (1941) in 47 per cent, and in Cimbäl's (1942) in 63 per cent

of the cases. According to Walther (1940 c), cases of urethritis (9 per cent) are more frequent than conjunctivitis (3.4 per cent). Kokko's (1945) series from Finland included only three cases of purulent urethritis, whereas 90 patients had "pain on micturition" and one half of them had also noticed that, although the output of urine was as usual, voiding was more difficult and the urinary stream poorer. As stated earlier (p. 15), Kokko's series consisted of cases observed during the acute stage of dysentery, and, consequently, they cannot all be considered Reiter's disease. Urethritis may occur as the initial symptom of the syndrome (Dorendorf 1917, Stettner 1917, Schittenhelm 1920, Beiglböck 1943, Hollander *et al.* 1945, Twiss and Douglas 1946, Vallee 1946, *etc.*), and it has been observed also as the only symptom (Dorendorf 1917, Arén and Lindgren 1945).

The urethral discharge seems to be less profuse than in acute gonorrhœa and it is in most cases observed only on pressure of the penis. It is reported to vary from sero-purulent to thick purulent and it may also contain blood. The urethral meatus is often described as swollen and red and its mucous membrane as slightly pouting (Singer 1915, Reiter 1916, Stettner 1917, Schittenhelm and Schlecht 1918, Sommer 1918, Stühmer 1921, Frühwald 1928, Balban 1934, Clemmesen and Kalbak 1938, Gounelle *et al.* 1941, Hollander *et al.* 1945, Jackson 1946, Twiss and Douglas 1946, Vallee, *etc.*). Microscopical examination has shown a large number of leucocytes but few epithelial cells. Bacteriological findings have been negative or only non-pathogenic organisms have been found (Singer 1915, Sommer 1918, Stühmer 1921, Frühwald 1928, Clemmesen and Kalbak 1938, Hollander *et al.* 1945, Feiring 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*).

Affections of the bladder have also occurred (Cahn 1916, Sick 1918, Hoff 1940, Cimbali 1942) and the series of some investigators have included even cases of cystitis of which a considerable part have been hæmorrhagic (Reiter 1916, Dorendorf 1917, Sommer 1918, Stühmer 1921, Holler 1941, Bauer and Engleman 1942, Beiglböck 1943, Colby 1944, Arén and Lindgren 1945, Haarr 1945, Miller and McIntyre 1945, Twiss and Douglas 1946, Pinck 1947). Bergmark (1946) has described two cases of cystitis more

closely, one of the patients having had a gonococcal urethritis about one month previously; recovery had been complete, however. In these cases hæmaturia, especially a terminal hæmaturia, was noted and in one of them also coagula. Cystoscopy revealed that the capacity of the bladders was 50 to 75 c.c., the mucous membrane was highly œdematous, bullous in places, partly covered by "fibrin", and bled easily.

As to renal disease Remlinger (1901) has noted acute nephritis once in connection with dysenteric arthritis and Schittenhelm and Schlecht (1918) similarly once. Remlinger's case was studied also patho-anatomically and the changes observable in acute glomerulo-nephritis were found. The nature of the disease in the latter case was not studied in detail. The authors only state that, besides a marked hæmaturia, albumin was found in the urine, and in the urinary sediment there were large numbers of white and red blood cells, a few granular casts and epithelial cells. In addition to pyelonephritis and cystitis, Colby (1944), in one case, diagnosed hydronephrosis and in another "renal dilatation" and hæmaturia. Slight albuminuria and pyuria were present also in one of Twiss and Douglas's (1946) cases, in Feiring's (1946) both cases, and in two of Zewi's (1947) cases. In the instance reported by Wrigley (1946) there was slight albuminuria but nothing pathological in the sediment. Otto (1940) and Hoff (1940) state that they have noted renal colic in a total of three cases.

Prostatitis has been recorded a few times in connection with Reiter's syndrome (Waelsch 1916, Wiedmann 1934, Clemmesen and Kalbak 1938, Bauer and Engleman 1942, Haarr 1945, Hollander *et al.* 1945, Miller and McIntyre 1945, Vallee 1946, Pinck 1947), and prostatic abscesses a few times (Colby 1944, Arén and Lindgren 1945). Tiemann (1932) describes a case of orchitis and Sick (1918) one of epididymitis. Ten out of Kokko's (1945) 555 patients with dysentery complained of testicular pain which was extremely persistent in some cases.

The presence of urethral strictures observed by Twiss and Douglas (1946) in one of their patients should be mentioned. This is attributed to a first attack of the disease two years pre-

viously. The urethritis involved also the prostate and the bladder, whereas the upper urinary tract was normal on intravenous urography.

According to most observers, the affections of the urinary system last for a few days or weeks, but may occasionally persist as long as four months (Stettner 1917, Stühmer 1921, Bergmark 1946, Sjöberg 1946, Twiss and Douglas 1946, *etc.*), and recurrence has been observed even several years after complete recovery (Stühmer 1921, Hollander *et al.* 1945, Twiss and Douglas 1946, Vallee 1946, *etc.*).

LESIONS OF THE NERVOUS SYSTEM

In connection with this syndrome symptoms have been observed also in the central and peripheral nervous system, and the commonest of these seems to be neuritis (Cahn 1916, Schittenhelm and Schlecht 1918, Steenis 1931, Holler 1941). In Walther's (1941) series neuritis occurred as a post-dysenteric complication in 0.7 per cent of the cases. Wilke (1943) observed polyneuritis both concomitant with the other symptoms of Reiter's disease and alone. The polyneuritis was usually localized in the nerves of the proximal muscles comprising the shoulders, the pelvic region and also the abdominal muscles (*e.g.* the *m. deltoideus*, *serratus*, *supra-* and *infraspinatus*, *ileopsoas*, *quadriceps*, *glutæus*). In severe cases of polyneuritis Wilke observed that the distal nerves of the extremities were also occasionally affected and then there were, besides muscular paralysis, disturbances of sensibility characteristic of the distal type of neuritis; in the proximal type sensory disturbances could be entirely lacking at first. Wilke (1943) further noted changes in the cerebrospinal fluid in severe cases; the albumin content was higher than normal but the number of cells was normal or only slightly increased. Zewi (1947) noted two cases of optic neuritis. — Neuralgias have also been described (Singer 1915, Rose 1916, Walther 1941, *etc.*). The most frequent localizations reported are the *trigeminus*, *occipitalis*, *frontalis*, *supraorbitalis*, *intercostalis*, *ulnaris*, *radialis*, *medianus*, *ischiadicus*, *saphenus*, and *tibialis*.

CARDIAC INVOLVEMENT

There is some disagreement as regards the occurrence of cardiac complications. Some observers state that heart complications are absent in Reiter's disease (Quinquand 1874, Raschewskaja 1935, Hoff 1940, Zewi 1946), while others hold the opinion that endocarditis and valvular disease do not occur, but myocarditis does (Dorendorf and Kolle 1916, Schemensky 1918, Steenis 1931, Otto 1940, Holler 1941). A few investigators have also reported cases of endocarditis. Thus Stettner (1917) comments on lesions of the endo- and myocardium. According to Rose (1916), Castin and Fradet have published a case of mitral disease complicating dysenteric arthritis and Trousseau a case of endo-pericarditis. Beiglböck (1943) reports a case of mild mitral endocarditis, and Bergmark (1946), in one instance, considers the diagnosis of endocarditis established. Gauster (1869) noted a left-sided exudative pleurisy once and, as an additional finding, exudative pericarditis as complications of post-dysenteric arthritis. A systematic electrocardiographic study of patients with dysenteric arthritis has not been made. However, a number of electrocardiographic tracings have been obtained by a few investigators; some of them noticed no abnormalities (Salvesen 1937, Kielland 1939, Walther 1940 b, Miller and McIntyre 1945, Twiss and Douglas 1946), while others observed changes which indicate myocardial damage (Beiglböck 1943, Bergmark 1946). In Vallee's (1946) case electrocardiographic changes appeared during the treatment: the P-R interval was prolonged to 0.26 second and there was at the same time a slight rise of the S-T segment in leads 2 and 3. In Feiring's (1946) two cases the P-R interval varied from 0.18 to 0.24 second in several tracings recorded during the treatment.

It should be added that Dorendorf and Kolle (1916) called attention to the occurrence of bradycardia and Schittenhelm and Schlecht (1918), Schemensky (1918), Hoff (1942), and Manson-Bahr (1943) to that of tachycardia in this disease. Schemensky (1918) attributes the tachycardia to slight toxic injury to the heart muscle or to nervous disorder. Walther (1940 b) states, on

the other hand, that tachycardia occurs as a late symptom in about 1 per cent of patients with dysentery. The tachycardia, which generally starts during convalescence on the 16th to 25th day after the onset of the disease, he considers a sign of an allergic phenomenon in the organism.

RESPIRATORY SYSTEM

Among diseases of the respiratory tract complicating Reiter's syndrome, cases of dry and exudative pleurisy have been described (Gauster 1869, Schittenhelm and Schlecht 1918, Sick 1918, Holler 1941, Cimbal 1942); the pleurisy has usually been mild (Schittenhelm and Schlecht 1918). In Gauster's (1869) case referred to earlier (p. 21) there was, in addition to a left-sided pleurisy, also an exudative pericarditis, but other instances suggestive of a possible polyserositis have not come to the author's attention. Further, some cases of bronchitis have been reported (Cahn 1916, Schittenhelm and Schlecht 1918). In Walther's (1940 c) series bronchitis occurred in 13.8 per cent of the cases. Schittenhelm and Schlecht (1918) reported some instances of epistaxis concurrent with the other symptoms and in the series of Gounelle *et al.* (1941) these amounted to 32 per cent. Gounelle ascribes the epistaxis to prolongation of the coagulation time. Cases of rhinitis and pharyngitis have also been noted (Feiring 1946, Vallee 1946).

DIGESTIVE SYSTEM

As stated already, diarrhœa is present in the great majority of cases. It cannot, however, be regarded as a symptom of Reiter's disease but should rather be looked upon as an antecedent disease mainly on the following grounds: (1) it occurs almost without exception before the onset of the cardinal symptoms of the syndrome, antedating them usually by some weeks, at times even months; (2) The diarrhœa in these cases has not differed in any way from the epidemic diarrhœa occurring on each occasion in the same locality. — Apart from this diarrhœa involvement of the digestive system seems to be extremely rare. Thus

only twice has a palpable spleen been reported (Reiter 1916, Schittenhelm and Schlecht 1918) and twice a spleen enlarged to percussion (Balban 1934, Pflieger 1937). At times jaundice has been observed together with dysenteric arthritis, but as its nature and course have not differed from ordinary catarrhal jaundice, it has evidently been only a coincidental disease (Schittenhelm and Schlecht 1918, Tiemann 1932, Hoff 1940).

OTHER LESIONS

Involvement of glands other than the sex glands already mentioned has been reported a few times. Thus Sick (1918), Manson-Bahr (1920 and 1943), Otto (1940), Hoff (1940), and Holler (1941) have noted parotitis, Sick (1918) and Kokko (1945) inflammation of the submandibular gland, Sick (1918) two cases of inflammation of the lacrimal gland and two of the mammary gland. In Reiter's disease the lymph nodes have also frequently been involved, enlargement of the axillary and inguinal nodes being observed (Moltke 1936, Usseglio and Zancan 1940), Bauer and Engleman (1942). Twiss and Douglas (1946) and Feiring (1946) have both published a case in which the cervical, axillary, epitrochlear, and inguinal nodes were enlarged. Microscopical section showed a non-specific type of hyperplasia of the inguinal lymph node (Twiss and Douglas 1946).

Besides redness of the urethral meatus other cutaneous changes have also been observed on the penis. Cases of balanitis have been described occasionally (Sick 1918, Clemmesen and Kalbak 1938, Cimbali 1942, Beiglböck 1943, Hollander *et al.* 1945, Wrigley 1946, *etc.*). Furthermore, typical eczema has been noted on the glans and the prepuce (Postma 1937, Beck 1937, Kuske 1939, Kruspe 1941, Hoff 1942, Hollander *et al.* 1945, Sargent 1945, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Vallee 1946). These lesions may appear as small, sharply margined erythematous spots covered with a brown crust (Kruspe 1941, Vallee 1946, Feiring 1946, *etc.*) or as small yellowish vesicles or superficial ulcerations occasionally with a narrow light-coloured

edge; the lesions may also be coalescent (Beck 1937, Twiss and Douglas 1946, etc.). Lesions of a similar kind may, according to Twiss and Douglas (1946), appear also in the conjunctivæ, the cornea, hard palate, pharynx, scrotum, and palms of the hands. Of other skin lesions may be mentioned hyperkeratotic eruptions on the extremities and the trunk (Rost 1911, Wiedmann 1934, Kuske 1939, Kruspe 1941, Hollander *et al.* 1945, Storm-Mathisen 1945, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Pinck 1947). Kuske (1939) states that these lesions are erythematous and papular at first, but later pustular efflorescences surrounded by a narrow inflammatory margin develop. Finally crusts arise which are hyperkeratotic in appearance and the eruption most closely resembles *rupia*. Histologic examination revealed parakeratotic hyperkeratoses, serofibrinous exudate, and large numbers of small pus cells. On the soles the lesion seems to appear as small pustules with hyperkeratosis of the overlying skin (Twiss and Douglas 1946), and the finger nails may be raised by hyperkeratotic collections. Changes in the nails appear at the same time. They become long, thickened and brittle, and the nail fold grows markedly (Rost 1911, Twiss and Douglas 1946). Urticaria has also been observed in dysenteric arthritis (Walther 1941, Holler 1941); erythema exsudativum multiforme (Cahn 1916, Rose 1916), and hæmorrhagic eruptions (Gaussel 1936, Cahn 1916, Schittenhelm and Schlecht 1918) are rare occurrences. In the mouth cavity lesions have appeared (*stomatitis aphthosa* and *ulcerosa*, glossitis) either associated with skin lesions or without them (Cahn 1916, Rose 1916, Schittenhelm and Schlecht 1918, Hoff 1940, Feiring 1946, Twiss and Douglas 1946). Local œdema has been described (Schemensky 1918, Sick 1918, Hoff 1940), and Holler (1941) considers it Quincke's œdema. A few cases of otitis externa have also been reported in connection with Reiter's disease (Steenis 1931, Wrigley 1946).

It is difficult to say whether all the skin lesions here enumerated can be ascribed to Reiter's disease, or whether they are concurrent lesions due to other causes. At any rate it should be borne in mind that there may be considerable difficulty in differentia-

ting Reiter's disease from *keratosis blennorrhagica* and from the so-called Stevens-Johnson syndrome.

FEVER

The fever in Reiter's disease seems to be subject to great variation. Thus there has been high fever in some cases, while in others only a slight rise of temperature has been observed and even afebrile cases have been reported (Huette 1869, Quinquand 1874, Kräuter 1871, Dorendorf and Kolle 1916, Dorendorf 1917, Schittenhelm and Schlecht 1918, Hoff 1940, *etc.*). The maximum axillary temperature most often reported is 39.5—40°C. (Schemensky 1918, Stühmer 1921). According to Rose (1916), the maximum axillary temperature varied from 37 to 37.4°C. in subacute polyarthritis in which the only symptom was articular pain, from 37.8 to 38.2°C. in acute monarthrititis, and from 37 to 39 and 39.5°C. in acute polyarthritis. In cases of "muscular rheumatic disease" Schemensky (1918) observed a rise of temperature to 37.5°C. in only one, the temperature being normal in the others. — As regards the nature of the fever it is reported that the remissions are generally great in the types with high fever, the temperature being in the morning 37°C. and in the evening 39—40°C., and the duration of the fever may vary from a few days to five months (Gauster 1869, Rose 1916, Reiter 1916, Stettner 1917, Sommer 1918, Stühmer 1921, Hollander *et al.* 1945, Jackson 1946, Twiss and Douglas 1946, *etc.*).

Opinions differ on the occurrence of sweating. Kräuter (1871), Balban (1934), and Cimbal (1942) report that in connection with the joint disease the patients experience severe sweating especially at night, but in Rapmund's (1874) series this was completely absent. Several others have observed that there is often no sweating or it is mild in degree (Dorendorf 1917, Schittenhelm and Schlecht 1918, Schittenhelm 1920), or occurs only at an early stage of the disease and often intermittently (Quinquand 1874). No definite mention of chills has been found. However, one of Gauster's (1869) cases started suddenly with chills; in the series of Hollander *et al.* (1945) no chills appeared.

BLOOD STUDIES

According to the literature, the sedimentation rate is generally increased and varies from 14 to 140 mm. in one hour by the Westergren method (Raschewskaja 1935, Moltke 1936, Postma 1937, Clemmesen and Kalbak 1938, Kielland 1939, Cimbald 1942, Stoia 1943, Beiglböck 1943, Miller and McIntyre 1945, Storm-Mathisen 1945, Bergmark 1946, Feiring 1946, Zewi 1947). Hollander *et al.* (1945) observed that an increased sedimentation rate generally became normal in about three months. In one of the cases reported by Twiss and Douglas (1946) the sedimentation rate remained normal in spite of ocular and urethral symptoms; during the period when articular symptoms were present the rate was increased.

Systematic studies of the blood picture seem to be fairly infrequent. On the basis of the few reports it appears that, in general, the red cell count has been normal (Moltke 1936, Clemmesen and Kalbak 1938, Beiglböck 1943, Miller and McIntyre 1945, Feiring 1946, Jackson 1946, Vallee 1946, Wrigley 1946). However, Twiss and Douglas (1946) have noted secondary anaemia in two cases and Storm-Mathisen (1945) in one. The white cell count has generally shown leucocytosis, but in some cases it has been normal. The number of leucocytes has varied from 4,800 to 21,000 per cu. mm. (Schittenhelm and Schlecht 1918, Stühmer 1921, Moltke 1936, Salvesen 1937, Postma 1937, Kielland 1939, Beiglböck 1943, Hollander *et al.* 1945, Miller and McIntyre 1945, Bergmark 1946, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Vallee 1946, Wrigley 1946, *etc.*). The differential count remained within normal limits except for an occasional eosinophilia or "shift to the left". Thus Moltke (1936) has once noted an eosinophilia of 6 per cent, Beiglböck similarly of 6 per cent, while in Twiss and Douglas's (1946) cases eosinophils varied from 2 to 28 per cent, the total number of leucocytes ranging from 9,700 to 19,300. The degree of the "shift to the left" has been slight, the values for the juvenile neutrophils varying from 2 to 3 per cent (Beiglböck 1943) and those for rod

neutrophils from 6 to 10 per cent (Postma 1937, Kielland 1939, Beiglböck 1943).

The blood protein and its fractions have been studied in five cases: the total plasma protein was 6.0, 6.5, 7.0, 7.45, and 7.77 per cent, the albumin being in the last four cases 4.6, 4.6, 3.66, and 3.02 per cent respectively, the globulin 1.8, 2.4, 2.94, and 4.75 per cent, and the fibrinogen in the last case 0.85 per cent (Salvesen 1937, Storm-Mathisen 1945, Feiring 1946, Vallee 1946). In rare cases some other special blood tests have been carried out: the blood urea, non-protein nitrogen, calcium, phosphorus, phosphatase, and the blood sugar have been determined and normal values obtained (Salvesen 1937, Clemmesen and Kalbak 1937, Miller and McIntyre 1945, Feiring 1946, Vallee 1946).

Serological studies have shown that the Wassermann reaction is negative in Reiter's disease (Frühwald 1928, Postma 1937, Salvesen 1937, Kielland 1939, Kruspe 1941, Beiglböck 1943, Feiring 1946, Vallee 1946). In Postma's (1937) series the Sachs-Georgi test was also negative, and the Kahn test taken occasionally has given negative results (Feiring 1946, Jackson 1946, Twiss and Douglas 1946). Also the gonococcal complement fixation test (gono-reaction, Kristensen) seems to give a negative result although control tests have been taken repeatedly after intervals of varying length, even over periods of several years (Kristjansen 1930, Moltke 1936, Salvesen 1937, Postma 1937, Clemmesen and Kalbak 1938, Kielland 1939, Beiglböck 1943, Hollander *et al.* 1945, Miller and McIntyre 1945, Vallee 1946, Twiss and Douglas 1946, *etc.*).

In Schittenhelm and Schlecht's (1918) series serum agglutination tests for dysentery proved negative and some sporadic cases have also given negative results (Miller and McIntyre 1945, Feiring 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*). However, some positive cases have been reported in which the patient's serum agglutinated dysentery bacilli of the Shiga-Kruse or Flexner group in titres of 1 : 80—1 : 600 (Markwald 1904, Cahn 1916, Sick 1918, Worms *et al.* 1927, Kielland 1939, Kruspe 1941, Beiglböck 1943, Young and McEwen 1947). In Cimbal's (1942) series of 50 examined patients this test was positive (1 : 100—1 : 800)

in 37, in 3 of whom there had been no diarrhœa. Positive agglutination tests for dysentery have been obtained also from the synovial exudate (Worms *et al.* 1927, Gounelle *et al.* 1941) in titres from 1:100 to 1:400 (Worms *et al.* 1927). In a few cases serum agglutination tests for typhoid, paratyphoid, and *B. abortus* were made, but agglutination could not be demonstrated (Kristjansen 1930, Kielland 1939, Miller and McIntyre 1945, Feiring 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*). In one instance Kruspe (1941) observed that the serum agglutinated *B. abortus* in titres of 1:400.

PATHO-ANATOMICAL CHANGES

Postmortem examination has been performed, according to the literature, in three cases. Remlinger (1901) noted in his two cases that the process in the knee joint was limited to the synovial membrane, although the disease had lasted for months. The synovium was thickened and its surface slightly opaque, the other soft parts and bone surfaces were of ordinary appearance. In one of these cases in which there had been an associated acute nephritis, each kidney weighed 350 grammes. The capsule was easily detached, the underlying surface appeared pale, greyish. The cortex was thickened. The medullary substance was dark red and its colour was clearly distinguishable from that of the cortex. Microscopical examination showed marked glomerulitis and focal hæmorrhages in the cortex as well as in the medullary substance. Fatty degeneration was observed in the cells of the tubulus contortus. Wepler (1942) has post mortem examined one case in which intestinal hæmorrhage was the cause of death. The hæmorrhage was due to the rupture of a submucosal blood vessel in the stomach; the cause of the rupture was not definitely revealed by microscopical study. The cartilages of the knee joint appeared normal and the articular cavity contained greenish yellow fluid. Microscopical examination revealed an œdematous synovium and disappearance of the superficial synovial cells. Lymphocytic infiltrates were present in the joint capsule and the periarticular tissue. The greater part of the cells

of the synovial exudate were polymorphonuclears. Nothing pathological was observed in the cartilage and the bone. In Wepler's opinion the process is non-specific and distinct from infectious and rheumatoid arthritis.

Bauer and Engleman (1942) performed an arthrotomy of the knee joint and observed formation of villi in the suprapatellar bursa. In a biopsy of the articular synovium the intima was found to be composed of several layers of cells and its lymphocytes and plasma cells were moderately increased, even the leucocytes to some extent. There were no corpuscular findings and no exudate. Throughout the subintimal layers there was also a mild, diffuse inflammatory cell infiltration. A marked hyperæmia was present in the synovium. Hollander and his co-workers (1945) also carried out an arthrotomy of the knee joint on a patient whose disease had lasted for eight months; the findings were as follows: Synovium greatly thickened, congested, and purple in colour. Lying on its surface were several small, circumscribed areas of white fibrinous-like material. The cartilages appeared normal. Microscopical examination showed intense inflammatory reaction limited to the superficial synovial layers. The synovium had large club-like projections which contained numerous dilated capillaries. Each projection was distended by a heavy lymphocytic infiltrate mixed with a few plasma cells and neutrophils. No exudate was observed. The intima was approximately six to ten layers deep. Only a few perivascular focal collections of lymphocytes and plasma cells were found. There were no new capillaries and the intense hyperæmia seemed to consist in dilatation of pre-existing capillaries. In the biopsy of an enlarged inguinal lymph node Twiss and Douglas (1946) found a moderate plasma cell infiltration and Storm-Mathisen (1945) chronic lymphadenitis.

TREATMENT

In the treatment of dysenteric arthritis the same principles have generally been followed as in the treatment of rheumatic fever. It has been noted, however, that salicylates and pyramidon

have little or no effect (Schittenhelm and Schlecht 1918, Schemensky 1918, Frühwald 1927, Kruspe 1941, Beiglböck 1943, *etc.*). Neosalvarsan, collargol, arthigon, and milk injections have also been used (Sommer 1918, Schittenhelm and Schlecht 1918, Stühmer 1921, Frühwald 1927, Stoia 1943), all with negative result. Only Beiglböck (1943) observed in ten cases treated with arthigon that a shifting of the pain to other joints stopped at least after the third injection, the pain subsided, the exudate diminished, and the conjunctivitis disappeared rapidly but the urethritis more slowly. In his opinion the rise of temperature seemed to be the essential feature of arthigon therapy; if there was no rise, the treatment seemed to be of no avail. Yet even in such cases a fever induced by pyriferein seemed to influence the course of the disease favourably. Rose (1916) reports that he has obtained very good results with anti-dysenteric serum and Schemensky (1918) states that serum treatment has given relief of pain and improved the mobility of the joints, although they did not seem to be less swollen, as in Rose's cases. Beiglböck (1943) and Stoia (1943), on the other hand, have obtained no positive results even with large doses of anti-dysenteric serum. Klemperer and Strisower (1920) report similar findings when using "Kruse's vaccine". Stoia (1943) states that he has obtained good results with injections of the patient's own blood treated with short waves, and with solganal. Sulphonamides (Beiglböck 1943, Hollander *et al.* 1945, Miller and McIntyre 1945, Twiss and Douglas 1946, Bergmark 1946, *etc.*) and penicillin (Hollander *et al.* 1945, Miller and McIntyre 1945, Bergmark 1946, Twiss and Douglas 1946, Feiring 1946, *etc.*) have hitherto proved of no effect in the treatment of Reiter's syndrome.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In Reiter's disease the diagnosis has not generally been considered difficult, as it is readily distinguished from other joint diseases by the associated symptoms. As already stated (p. 24), there may occasionally be considerable difficulties in differentiating the condition from *keratosis blennorrhagica* and the

Stevens-Johnson syndrome. This is chiefly due to the circumstance that, most recently, cases of Reiter's disease have been observed with skin lesions similar to those seen in *keratitis blennorrhagica* (Lever and Crawford 1944, Hollander *et al.* 1945, Twiss and Douglas 1946, Feiring 1946, Jackson 1946) and that, on the other hand, cases of the latter disease have occurred in which urethritis, arthritis and dermatitis have been accompanied by inflammation of the eyes (Lojander 1928, Chambers and Koetter 1933, Combes *et al.* 1940). Although a careful history-taking and the gono-reaction may often decide the diagnosis, it seems that the exact correlation of the two diseases is not yet clear. Freireich, Schwartz and Steinbrocker (1947) consider that they might be variants of the same disease and that gonorrhœal infection in *keratitis blennorrhagica* might be "a predisposing agent in the causative process actually producing pictures of both diseases and their variants". Stevens-Johnson's or Behcet's syndrome, on the other hand, comprises an aphthous or ulcerating stomatitis, ulcerations in the genitalia or around the anus, at times also urethritis, eye lesions, such as conjunctivitis, iritis, retinitis, and even hypopyonuveitis. In most cases there are also skin lesions, generally of the type *erythema exsudativum multiforme*. In many instances recurrences are noted. As some of these symptoms may be lacking and, on the other hand, also inflammatory joint disease may occur (Halonen and Klemola 1947), it is possible that a clinical picture resembling Reiter's syndrome may develop in certain cases.

PROGNOSIS

The prognosis *quo ad vitam* is good in Reiter's disease; up to the present it has not as such led to death in a single case. According to Huette (1869), earlier observers have reported cases which ended fatally, but the uncertainty of the diagnosis and of the causal connections make it improbable that these data can be seriously considered. In general the disease does not cause permanent or disabling changes in the affected organs. Yet there have been a few cases of permanent damage to the eye (Vallee

1946) and of ankylosis of the joints (Paetzel 1928, Raschewskaja 1935, Lever and Crawford 1944, Twiss and Douglas 1946, Vallee 1946), and one case of urethral strictures has been reported (Twiss and Douglas 1946).

DURATION AND RECURRENCE

Recovery is usually spontaneous. The duration varies in the reports of different observers, being generally, however, two to five months. Recurrences (*Cf.* p. 14) are seldom reported in the literature apparently because conditions have made sufficiently long observation of the cases impossible (most of the reported cases occurred in soldiers during World Wars I and II). Recurrence was noted in Freund's (1928) case ten years, in Storm-Mathisen's (1945) case seven and twelve years, and in one of Twiss and Douglas's (1946) cases two years after the initial illness. In Kardung's (1941) case there were several recurrences over a period of 15 years, in Sjöberg's (1946) case over a period of 5 years, and in Vallee's (1946) case of 16 years. Hollander (1946) states that recurrences appeared in 15 per cent of his cases.

ÆTIOLOGY AND PATHOGENESIS

Although a great number of studies have been published the ætiology and pathogenesis of Reiter's disease are still largely obscure. On the other hand, many positive observations have also been made on which future studies may be based.

The majority of researchers have held the opinion that Reiter's syndrome is causally closely related to dysentery (Huette 1869, Korczynski 1874, Dorendorf 1917, Schittenhelm and Schlecht 1918, Kruspe 1941, Walther 1940 c) or to other enteritic infections (Singer 1925, Tiemann 1932, Musger 1934, Pflieger 1937) which in most instances precede the essential symptoms of the syndrome. Yet — especially judging from German and American reports — it is evident that in some of the cases there has never been a dysentery or enteritis; therefore it has also been assumed that dysentery is not the sole, although perhaps the most usual cause of Reiter's syndrome. In the cases without diarrhœa it has

been supposed that the infection may enter by way of the genitalia (Waelsch 1916, Michael 1917, Paetzel 1928, Kristjansen 1930, Beck 1937, Thesleff 1937, Kuske 1939, Kardung 1941, Haarr 1945). Other portals of entry, for instance dental foci (Stoia 1943), furuncles (Junghanns 1918) *etc.*, have been more rarely suggested.

In the cases without diarrhœa the disease has been assumed to spread for instance through sexual connection (Waelsch 1916, Kristjansen 1930, Beck 1937, Löfgren 1943). In this respect Kristjansen's case is of particular interest. The patient developed a non-specific urethritis and arthritis one month after intercourse with a girl who was known to suffer from vaginal discharge, which had repeatedly proved negative for gonococci. The girl also had a relationship with another man who also acquired a non-specific urethritis, though without arthritis.

Reiter's finding of a spirochæte seems to have aroused particular interest and caused special investigations with a view to revealing the ætiology of the syndrome. Reiter (1916) made blood cultures from his patient in blood ascites broth and found in a two-day-old culture an organism which he believed to be a spirochæte; its movement was characterized by "a boring rotation and no flexion". For this reason Reiter called it *Spirochæte forans*. Mice inoculated with this culture died suddenly on the 8th to 10th day. On guinea pigs the culture had no effect and neither in these nor in mice was this spirochæte subsequently demonstrated. Reiter, however, believed that he had found the causative agent and therefore proposed *Spirochætosis arthritica* as the name of the syndrome. Later it was suggested that the so-called spirochæte of Reiter may not have been the causative organism but an incidental cultural finding (Sick 1918, Stühmer 1921, *etc.*). Besides Reiter, Macfie (1917) has only once found spirochætes in the urethral pus.

There have been other noteworthy bacterial findings. Worms *et al.* (1927) report that in stained specimens of aspirated synovial fluid in four severe cases they found a great number of polynuclear cells and clumps of "gram-negative cocci", but cultures yielded no growth. The aspirated fluid agglutinated dysentery bacilli in titres of 1 : 100—1 : 400. Musger (1934) obtained a non-

hæmolytic streptococcus from a blood culture; he assumed it to be an enterococcus and the causative agent of the disease. Pflieger (1937) also ascribed the condition to an enterococcus which he isolated from the patient's urine, whereas the blood culture was negative. Vallee (1946) states that in one case culture of the patient's urine was positive for the enterococcus. According to Posselt (1928), Elsworth once found Shiga-Kruse's bacillus in the synovial fluid in a case of dysenteric arthritis, and Stoia (1943) reports that Morenas and Besson discovered it in the blood and in the synovial fluid. Except for these infrequent positive bacterial findings, cultures of blood, urine, and synovial fluid have generally been negative; cultures of the urethral, conjunctival and prostatic discharge have also consistently failed to reveal any pathogenic organisms (Gaussel 1896, Remlinger 1898, Junghanns 1918, Schittenhelm and Schlecht 1918, Stühmer 1921, Frühwald 1928, Musger 1934, Beck 1937, Clemmesen and Kalbak 1938, Bauer and Engleman 1942, Hollander *et al.* 1945, Kokko 1945, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*). Steenis (1931) reports two stool cultures and Sick (1918) one such culture which were positive for Shiga-Kruse's bacillus when symptoms of the syndrome were already present. Young and McEwen (1947) report stool cultures positive for *B. paradysenteriae* in three cases.

Dienes and his associates (Dienes and Smith 1942, Dienes, Smith and Ropes 1946) have recently made a highly interesting bacteriological finding. They isolated pleuropneumonia-like organisms from the prostatic discharge of four patients, from the urethra of one, and from the aspirated synovial fluid of one. These organisms have been found earlier in rats suffering from arthritis, in the conjunctiva of normal mice, and in an infectious disease called agalactia occurring in sheep, the symptoms of which are conjunctivitis, arthritis, and inflammation of the udders and testes. The same organisms have been discovered in cultures of vaginal discharge of women suffering from leucorrhœa and recently also in cultures of urethral discharge obtained from men with a non-specific urethritis (Beveridge 1943). These microorganisms are extremely pleomorphic, their reproduction is both

sexual and sexless, and they change their form. In one form they are filterable, like viruses, in another they may exactly resemble bacteria, also as regards conditions of growth.

It is naturally too early to draw far-reaching conclusions from the studies of Dienes, yet the value of Reiter's and Macfie's observations of spirochaetes will be quite different if Dienes's findings are confirmed. In any case the work of Dienes requires serious consideration in all future studies of Reiter's syndrome.

It may be added that the consistently negative results obtained in numerous bacteriological tests have given rise to the hypothesis of virus causation (Beck 1937, Löfgren 1938, 1943 and 1946, Arén and Lindgren 1945).

Some investigators have assumed that the syndrome is caused by metastases (Vossius 1904, Dorendorf 1917, Brugsch 1931, *etc.*) or by toxins produced by the dysentery bacillus (Remlinger 1898, Dorendorf 1917, Steenis 1931, *etc.*). The observation, rare as it is, of *B. dysenteriae* also in the patient's blood in dysentery would seem to suggest the former possibility. Thus Posselt (1928) found in the literature a total of 140 cases in which blood cultures yielded *B. dysenteriae*. However, these organisms were in most cases found only at the onset of dysentery or during the period of incubation. In the cases described above (p. 34) *B. dysenteriae* was obtained from the synovial fluid; this seems to support the theory of a metastatic origin. Schittenhelm and Schlecht (1918) consider that the disease cannot be ascribed to dysenteric toxins, as it appears at a time when the bowel wall ought already to be healed and consequently there should be no more toxin in the body, and as it also occurs in cases in which enteritic symptoms are entirely lacking. In their opinion there would still remain the possibility of an enteric infection caused by other kinds of spores whose toxins might play a part in the causation.

Attempts have been made to explain the pathogenesis of Reiter's disease on the basis of the theory of allergy, analogously with that of rheumatoid arthritis (Löfgren 1938, Walther 1940 a, b, c, 1941, *etc.*). Schittenhelm and Schlecht (1918) are opposed to this opinion, as they observed no allergic reaction when dysentery patients were injected with dysenteric vaccine or toxin.

Walther (1940 a, b, c, 1941) considers it likely that dysenteric arthritis is an allergic disease but does not regard it simply as a complication of dysentery, as it often appears already in the first week of disease, even one to two days before the enteritic symptoms, at a time when the causative agent of dysentery cannot yet have sensitized the organism; he supposes that some other antecedent disease — a previous dysentery, rheumatic fever, scarlet fever, gonorrhœa, sinusitis, angina, *etc.* or a focal infection, might have sensitized the organism beforehand and that the dysentery, encountering this already "charged" system, would — in a way — make the disease "burst out". "*Frürrheumatismus*", accordingly, would be a parallergic reaction appearing chiefly as arthralgias and myalgias, whereas "*Spätrheumatismus*", commencing in the third to fourth week of disease and often as a severe polyarthritis, would probably be accounted for by a specific allergic reaction.

Finally there are the skin reaction tests carried out by Storm-Mathisen (1945) with synovial exudate and lymph node emulsion obtained from a patient with Reiter's disease. Within forty-eight hours there was a reddish infiltrate in the area of injection in the patient himself and in four others with the same disease. In the control cases the result was negative. On account of the small number of cases and in the absence of required additional studies it seems that no conclusions can be drawn as to the specificity of the reaction.

OBJECT OF THE INVESTIGATION; THE PROBLEM

The review of the literature given in the previous chapter will have shown that the disease known as dysenteric arthritis or Reiter's syndrome has attracted the interest of investigators for several decades and that numerous studies have been published dealing from different aspects with the clinical picture, ætiology, pathogenesis, prognosis, and treatment of this disease. Agreement has already been reached on many questions concerned with this syndrome, but — on the other hand — many others of essential importance still remain obscure. A study of the disease has evidently been rendered more difficult by its comparatively rare occurrence and the fact that most cases have appeared in war time, when conditions have been particularly favourable for the spread of dysentery but the opportunities for scientific study also more limited than in times of peace.

Although observers agree in all essentials as to the clinical picture of Reiter's disease, it is notable that opinions vary regarding questions so important as cardiac and pleural involvement and the tendency of the disease to recur. Different data have also been published on questions of less importance, for instance the migration and external manifestations of the arthritis, the occurrence of skin lesions, sweats *etc.* It is also noteworthy that, up to the present time, there have been no systematic studies of the blood picture, electrocardiogram *etc.* in this disease. — Most of the disagreements and deficiencies here mentioned seem to be due to the small number of cases generally dealt with in the publica-

tions, a series often comprising only from one to ten cases; thus the observer may have had a too limited view.

However, the greatest disagreement seems to prevail on the ætiology and pathogenesis. While some consider that dysentery is the basic disease and can be so even in cases without dysentery, others hold that Reiter's syndrome is no disease *sui generis*, but a syndrome caused by different infectious diseases and infections. It has also been ascribed to Reiter's spirochæte, virus infection, and most recently, to pleuropneumonia-like organisms. As regards the pathogenesis Reiter's syndrome has been ascribed to bacteria, bacterial metastases or toxins, invasion being by way of the intestines, the urethra or some other point, but it has also been regarded as an allergic disease.

Thus our knowledge of Reiter's disease is still defective in many respects and further study of the subject seems necessary and desirable. As there were a great number of cases — almost an epidemic — in Finland in 1943 and especially during the widespread dysentery of 1944, a closer study and the publication of the material (344 cases) thus obtained has seemed advisable, the more so as no more extensive series than this has hitherto been published.

On the basis of what has been stated in the review of the literature the writer has here chiefly sought an answer to the following questions:

1. *What is the clinical picture and prognosis of Reiter's disease?*
2. *Does the material available throw additional light on its ætiology and pathogenesis?*

MATERIAL AND METHODS

The present series comprises a total of 344 cases (see Table 1). Of these the hospital reports of 10 have been lost, so that the actual material consists of 334 cases. The great majority (322 cases) are from the Defence Forces and were observed in 1943 and 1944. There are also 22 civilian cases from 1945 and 1946, of whom 13 were treated at Medical Clinic II of the University of Helsinki, one at the Children's Clinic, one at the Out-Patient Department for Internal Diseases, and two cases at the Medical Department of the Kivelä Hospital; five cases are from the writer's private practice.

In the autumn of 1943 a Corporal was admitted to the 31st Field Hospital with a severe, sterile conjunctivitis and urethritis, and indefinite pain in the knees. The case aroused surprise, until — after the knee joints had swollen — Reiter's syndrome was diagnosed. Similar cases appeared later in other places and the patients were collected, at the end of 1943, at Medical Clinic II of the University of Helsinki which had been converted into a War Hospital. During 1944 such cases were collected at the 56th War Hospital at Nokia; Medical Clinic II had been evacuated to this place in February 1944. On the Karelian Isthmus, where most of the cases occurred, the patients were first collected chiefly at Field Hospital 31 where some mild cases were treated and then returned fit for duty to their units. Those requiring prolonged treatment were evacuated to War Hospital 56, and at the end of 1944 those still in need of treatment were transferred to the 10th Hospital for Disabled Servicemen at Tampere. Some of these patients were later admitted to Medical Clinic II in Helsinki and a few to the Hospitals for Disabled Servicemen in their communal areas.

During all this time Prof. P. Soisalo was the Head of Medical Clinic II and War Hospital 56 and he personally investigated the cases and supervised the examinations and therapeutical measures. The writer too had the opportunity of examining and personally treating the greater number of the patients during the entire course of their illness, and each patient at least at some stage, while working at Field Hospital 31, War Hospital 56, the 10th Hospital for Disabled Servicemen, and Medical Clinic II. The methods of study and observation have thus been most uniform. A great advantage was the well-equipped laboratory of the hospital, although war-time conditions caused certain difficulties and prevented the use of some planned methods of investigation. All the patients were subjected to the closest possible clinical examination and the course of the disease was followed from day to day. The methods used will be described when discussing the results.

Table 1 shows the year the illness started and the age and sex distribution of the patients.

TABLE 1
YEAR OF ONSET WITH AGE AND SEX OF PATIENTS

In 1943	11 cases		
„ 1944	311 „		
„ 1945	21 „		
„ 1946	1 „		
Total	344 cases		

Age, Years	Men	Women	Total
2	1	—	1
12—15	3	—	3
16—20	29	5	34
21—30	166	12	178
31—40	102	8	110
41—50	9	8	17
55	—	1	1
Total	310	34	344

The material is in some measure one-sided in that it comprises for the most part previously healthy 18 to 40 year old men fit

for duty and women of about the same age and physical condition who served in the forces, but only few civilians. The figure in the preceding table, consequently, do not give an all-over picture of the question concerned.

The sero-bacteriological studies were carried out partly in the Department of Serology and Bacteriology in the University of Helsinki, partly in the Bacteriological Laboratories of the Defence Forces, and, in addition, a considerable part of the bacteriological tests and cultures were made in the laboratories of each hospital. Studies of vitamins were carried out in the Department of Medical Chemistry of the University of Helsinki.

THE CLINICAL PICTURE OF REITER'S DISEASE

THE THREE CARDINAL SYMPTOMS

The incidence of the three cardinal symptoms of Reiter's disease, i.e. of articular, ocular, and urogenital affections, is shown in Table 2 where + denotes that the organ is affected, and — that it is unaffected.

TABLE 2
OCCURRENCE OF THE THREE CARDINAL SYMPTOMS OF THE SYNDROME

Joints	Eyes	Urogenital system	Total No. of cases	%
+	+	+	233	69.8
+	+	—	56	16.8
+	—	+	24	7.2
—	+	+	4	1.2
+	—	—	12	3.5
—	+	—	5	1.5
—	—	+	0	0
Total 325	298	265	334	100
% 97.3	89.2	79.3		

As seen from Table 2, the complete triad — affections of joints, eyes, and urethra — is the most common type in the author's series which in this respect corresponds to several earlier publications. On the other hand, this series differs from some reports published earlier in that the incidence of ocular and urogenital involvements is high (Cf. pp. 16 and 17). Cases with only urethral lesions are entirely lacking in this material which, however, may

depend also on the fact that such cases were not sent to the hospitals mentioned above but treated elsewhere.

In the great majority of the cases (69.1 per cent) the onset was monosymptomatic; the initial symptom was urethritis in 23.9, arthritis in 23.3, and conjunctivitis in 21.9 per cent of the cases. In less than 1/4 of the cases the onset was bisymptomatic, the two initial symptoms appearing during the same day. Involvement of eyes and urinary system was the most common combination, the next in order lesions of eyes and joints, while the urinary tract and the joints were seldom simultaneously involved. Less than 8 per cent of the cases showed the entire triad at the onset; all the three cardinal symptoms appearing on the first day of the disease. Each of the three cardinal symptoms occurred on the first day of the disease, alone or in any combination; eye involvements in 48.6 per cent, urethritis in 47.3 per cent, and arthritis in 42.8 per cent.

The present material corresponds to those reported by Doren-dorf (1917), Schittenhelm (1920), Beiglböck (1943) *etc.* in that the disease may begin with any of the three essential symptoms; it is not, however, possible to compare numerical data because they are lacking in earlier investigations.

In the cases with only one or two initial symptoms some new essential symptom could appear as late as more than a hundred days after the onset. Thus a case appearing mono- or bisymptomatic at first could later become bi- or trisymptomatic. In the great majority of cases (71.4 per cent), however, all the cardinal symptoms appeared during the first ten days after the onset of the syndrome. This is seen from Table 3 which shows the time — in ten-day periods — during which the complete triad or two symptoms of it developed.

In the writer's series of Reiter's disease all three cardinal symptoms were thus present in 69.8 per cent of the cases, 25.2 per cent showed two symptoms, and 5.0 per cent only one symptom. Cases with only urethral lesions were not observed. Any of the three cardinal symptoms, or any combination of the three, were present at the onset. More than 2/3 of the cases had only one initial symptom, less than 1/4 had two initial symptoms, and

less than 8 per cent showed the complete triad at the onset. In about 71 per cent of the cases a clinical picture with three or two symptoms developed during the first ten days of the disease, in the others later, even as late as one hundred days after the onset.

TABLE 3
PERIOD DURING WHICH THE COMPLETE TRIAD OR TWO SYMPTOMS
OF THE SYNDROME EVOLVED

Days	No. of cases	%
1—10	224	71.4
11—20	43	13.7
21—30	20	6.4
31—40	12	3.8
41—50	7	2.3
51—60	2	0.6
61—70	2	0.6
71—80	1	0.3
81—90	2	0.6
101—110	1	0.3
Total	314 ¹⁾	100

¹⁾ Three cases are omitted because the clinical report did not reveal the length of this period.

ARTICULAR INVOLVEMENT

In addition to the usual methods of examination, a new one has been used to discover the presence of fluid in the knee joint. This method, of which the author has found no description in the literature, seems to be suitable in cases in which the amount of fluid is so small that ballottement of the patella is difficult to notice. The method is as follows: The patient lies on his back relaxed, the knee joint extended and its front and inner aspect well illuminated. By moving the patella the examiner makes sure that the patient does not strain the femoral muscles, and then presses the medial excavation of the knee until any fluid which has collected there is pressed out. Immediately after that the area between the lateral excavation and the upper recess is pressed; all the fluid in the joint now flows back to the medial side and this is recognized by a distinct swelling of the medial excavation, a visible reflux of fluid. The simplest way of carrying out the test is as follows: the examiner grasps the knee of the patient from the proximal side so that the patella remains between the thumb and the forefinger. The medial excavation is pressed with the thumb and all four fingers, the area of the lateral excavation and the upper recess with

the palm. If the exudate is old it may move so sluggishly to and fro that alternate pressure on the medial and lateral excavation may be required several times until there is a reflux of fluid. This phenomenon is probably caused by the greater viscosity of old exudate or by adhesions that may have developed in the joint cavity and which at the beginning of the test may prevent the moving of the fluid.

Joint manifestations were present in 325 cases (97.3 per cent). Of these 316 (97.2 per cent) were polyarthritic and only 9 cases (2.8 per cent) monoarthritic. The arthritis generally began in one or several joints with tenderness upon movement or touch. Some patients felt only stiffness on moving the joint. Spontaneous pain, too, appeared in most cases after a day or two. In some patients (17.5 per cent) the joint affection was of arthralgic type during the whole disease, but in the majority (82.5 per cent) it was associated with articular swelling; all the affected joints or only some of them became swollen while the others remained of arthralgic type. Table 4 shows the distribution of the material into three such groups as well as the relation between poly- and monoarthritis.

TABLE 4
ARTICULAR INVOLVEMENT

	Arthritis	Arthralgia	Arthritis and arthralgia combined	Total
Polyarthritic	44	55	217	316 = 97.2 %
Monoarthritic	7	2	—	9 = 2.8 %
Total	51	57	217	325
	15.7 %	17.5 %	66.8 %	

In Table 5 is seen the frequency of involvement of different joints, the incidence of swelling and arthralgia, and the changes in skin colour observed in the swollen areas. The frequency of joint involvement corresponded largely to data in earlier reports (Cf. p. 13), but in the present series there was no noticeable difference between the joint manifestations of the right and left side, as pointed out by Huette (1869).

TABLE 5

FREQUENCY OF JOINT INVOLVEMENT, RELATION BETWEEN ARTHRITIS AND ARTHRALGIA, AND ALTERATIONS IN SKIN COLOUR IN 324 CASES

Joint	Total No. of affected joints	Arthritis	Arthralgia	Joints with changes in skin colour
Knee	448 = 25.4 %	315	133	—
Ankle	286 = 16.2 %	196	90	62
Toes ¹⁾	142 = 8.0 %	109	33	57
Shoulder	137 = 7.8 %	6	131	—
Wrist	114 = 6.5 %	61	53	6
Fingers ¹⁾	114 = 6.5 %	76	38	19
Metatarsal ¹⁾	109 = 6.2 %	83	26	34
Sacrum ¹⁾	106 = 6.0 %	—	106	—
Elbow	86 = 4.9 %	14	72	3
Hip	74 = 4.2 %	2	72	—
Vertebral, lumbar and thoracic ¹⁾ .	50 = 2.8 %	—	50	—
Vertebral, cervical ¹⁾	27 = 1.5 %	—	27	—
Metacarpal ¹⁾	25 = 1.4 %	19	6	6
Sternoclavicular ..	15 = 0.8 %	11	4	—
Acromioclavicular	13 = 0.7 %	—	13	—
Temporo-mandibular	12 = 0.7 %	—	12	—
Sacroiliac	7 = 0.3 %	1	6	—
Tibiofibular	1 — (0.1 %)	1	—	—
Total No. of joints	1766 = 100 %	894	872	187

¹⁾ Considered as one joint although several joints were affected.

In about 60 per cent of the cases the different joints became involved within 20 days calculated from the day the first joint became affected to the day the last became involved. However, there were cases in which new joints became involved even several months after the onset of the first articular symptoms. This is illustrated in Table 6 showing the distribution of the cases according to ten-day periods.

TABLE 6
PERIOD DURING WHICH THE DIFFERENT JOINTS OF A PATIENT
BECAME INVOLVED

Time in days	No. of cases
1—10	112
11—20	69
21—30	37
31—40	28
41—50	14
51—60	10
61—70	7
71—80	4
81—90	3
91—100	4
101—110	—
111—120	4
121—130	2
131—140	5
Ca. 7 months	2
„ 11 „	1
Total	302

In the majority of cases the tenderness of the joints was relatively mild. The patient was able to move the swollen joints and to stand. There was generally only partial limitation of movement; in some cases the joints could even be freely moved and pain was felt only at the extreme range of motion. Active movements were always more painful than the passive. In a few patients the tenderness was so severe that the joints could be moved only very little, and the pain in the joints resembled greatly that seen in gonorrhœal arthritis. These cases also showed a great tendency to contractures and muscular atrophy. Spontaneous pain in the joints was often very marked at the onset and seemed to be due, in most cases, to distention of the bursæ or of the joint capsule by the heavy exudation. In some patients, on the other hand, the spontaneous pain was slight and was felt particularly at night. In the morning several patients complained of a stiffness of the joints which, however, decreased

considerably during the day, or even disappeared entirely. Swelling of the joints generally appeared during the first days of the disease simultaneously with the pain and tenderness, but in some cases there was pain and tenderness even several weeks before the joints became swollen. Swelling of the knee joint was invariably due to the presence of exudate in the joint cavity or the bursæ and not to periarticular œdema. In the elbow joint exudate was found in only three cases. In the other joints fluid was not noted on clinical examination, and the swelling then seemed to consist of a periarticular œdema which varied somewhat in severity and firmness according to the localization and the individual. Thus intense swelling often occurred on the ankle joint where the region of the medial or lateral malleolus might be swollen, the other side of the joint appearing normal. On the dorsum of the foot and the back of the hand the œdema was also intense and softer than elsewhere. In the finger and toe joints spindle-shaped swelling was observed. In the knee joint a large amount of exudate generally developed in the early stage of gonitis, causing intense and painful distention. The exudate was yellowish with a slight tinge of green, viscous, and usually somewhat turbid. Its specific gravity varied from 1.020 to 1.022 (six cases) and the range of the pH was from 7.5 to 10.0 (14 cases). In 2/3 of the examined patients (30 cases) the exudate contained between 4 and 5 per cent albumen, the minimum being 1 per cent and the maximum 12 per cent (Esbach). In the majority of the cases the cells of the exudate consisted chiefly of neutrophil granulocytes, their percentage amounting even to 90 per cent. In some instances, however, lymphocytes predominated, varying from 57 to 74 per cent. Monocytes represented 1 to 2 per cent. The amount of eosinophil cells ranged from 0 to 53 per cent (seven cases).

Further, it was observed that certain joints were swollen in none of the cases, some very seldom, others again comparatively often, and that the swelling in certain joints consisted of a periarticular œdema, while in others the presence of exudate seemed responsible for it. This variety seemed to depend mainly on anatomical construction of the joint and on the quantity and quality

of the surrounding tissues. In the knee joint, for instance, there are large bursæ which communicate with the joint cavity and are able to hold a large amount of exudate; the knee joint also contains places where the tissues surrounding the joint readily yield to pressure from the inside. An articular structure of this kind facilitates the formation of exudation, as is seen for instance in the fact that exudate develops more slowly if, after aspiration, a tight bandage is applied. On the other hand, in a joint surrounded by unyielding tissue like tendons and aponeuroses a recognizable exudate cannot develop, and the exudative process leads rather to a periarticular swelling. If the joint lies deep in the tissues and especially if covered with muscles — as for instance the joints of the vertebral column — even this œdema cannot be clinically recognized.

In 187 articulations (Table 5) changes occurred in the colour of the skin, but only in five cases (twice in the knee and three times in the ankle) was the skin definitely hot. The colour alterations occurred in the swollen areas where the skin appeared dirty grey, although a purple or reddish component was often observed at first. In addition to swelling and a purple colour, numerous petechiæ appeared in one case in the ankle area and on the dorsum of the foot, lasting for 17 days. — Unfortunately, no studies of the blood coagulation were carried out in this case.

X-ray examination of the different joints was made in 76 cases, altogether 156 times. The knee was examined 67 times, ankle and metatarsal joints 53, wrist and metacarpal region 11, elbow 6, fingers 6, shoulder 5, and toes 4 times, hip twice, heel and cervical vertebræ both once. In the great majority of cases (66 in number) the examination was carried out within one month after the particular joint had become involved; in only nine patients within two to four months, and in one case one year after the disease began. In none of the cases were the roentgenological findings abnormal. In this respect the present material differs from earlier reports (Cf. p. 15), but this is probably due to the fact that X-ray examination was carried out at a time when roentgenological changes were not yet present. Because of

a shortage of films it was unfortunately not possible to submit our patients to follow-up examinations.

The present series resembled those reported earlier in that the pain in the affected joints was persistent and did not move from joint to joint, as is characteristic of rheumatic fever (*Cf.* p. 14). The amount of exudate and the severity of the symptoms varied to some extent, but generally the disease remained localized to the joints once involved and disappeared only gradually. In some instances the pain and tenderness in a particular joint, or even several, lasted only for a few days, but the more intense symptoms with the associated swelling were generally localized to a single joint or a few joints and persisted for a long time. Several patients complained of increased pain and tenderness of the affected joints in cold and wet weather.

MUSCLE AND TENDON INVOLVEMENT

The articular symptoms were accompanied by tenderness and pain in the scapular region in 45 cases, in the side in 26, the muscles of the limbs in 26, the heel in 13 (once associated with swelling), the Achilles tendon in seven (five associated with swelling), the tuberosity of tibia in five, and the spina iliaca anter. superior in three cases. The series included no cases showing the single symptom of muscular pain. The pain in all the locations mentioned was usually mild and troubled the patients especially at night, thus disturbing their sleep. The tenderness felt by the patients in these areas caused more discomfort. It could prevent deep breathing, render walking difficult and so on. The roentgenological findings in these cases were negative, also in one case in which the insertion of the Achilles tendon had been swollen and tender for 4 ½ months. The symptoms described above usually lasted for a comparatively short period, a few days or weeks. An exception was the case in which the insertion of the Achilles tendon was affected; the region was definitely swollen and slightly tender on pressure even two years later.

OCULAR INVOLVEMENT

The series of 334 patients included 298 cases (= 89.2 per cent) with eye symptoms. Table 7 shows the types of ocular involvement.

TABLE 7
OCULAR INVOLVEMENT

Diagnosis	No. of cases	Remarks
Conjunctivitis acuta	239	11 unilateral cases
Keratoconjunctivitis	13	7 " "
Iritis	11	7 " "
Keratoiritis	10	7 " "
Ulcus simplex corneæ	4	
Iridocyclitis	1	
Total	278	
Feeling speck in eye, epiphora and purulent discharge without noticeable redness	20	
Total No. of cases	298 = 89.2 %	

As seen from Table 7, the majority of the eye affections were diseases of the conjunctiva and obviously conjunctivitis had been present also in all others. In only two cases was irido-conjunctivitis the primary ocular diagnosis, and in one kerato-conjunctivitis. Even these were not noted until about five days after the onset of the eye symptoms. In all other cases involvement of the iris and the cornea was preceded by a conjunctivitis which had either become entirely asymptomatic or at least improved considerably in between. The asymptomatic interval varied from ten days to 17 months (*Cf.* p. 78). These cases are not included in the group of conjunctivitis in Table 7; they have been separated into a special group of iridic or corneal involvement. Examination of the eye grounds was carried out in very few cases of conjunctivitis but regularly when the iris and cornea were affected. The eye grounds were normal in all examined cases.

The conjunctivitis was bilateral in all except 11 cases. In most cases (4/5) the conjunctivitis began in both eyes at the same time. In about 1/5 of the cases the other eye became affected later, generally after one to two days, but occasionally

after more than two months. The first symptoms of conjunctivitis were a feeling of something in the eye, smarting, photophobia, and epiphora. This was soon attended by redness of the conjunctivæ and a mucopurulent discharge. The lids often stuck in the morning. Swelling of the lids appeared often but was generally slight; in few cases was intense swelling observed. The eyes of one patient were absolutely "walled up" owing to very intense swelling as far as the anterior part of the auricle, and swelling remained intense for five days. Both the *conjunctiva palpebræ* and *bulbi* were a deep cranberry red and had a velvety surface. The redness varied in degree, being rather slight in some cases but mostly intense and occasionally attended by a marked chemosis, which partially covered the cornea. In some instances the symptoms were milder in one eye than in the other during the whole course of the disease. This characteristic colour of the conjunctiva and its velvety surface were most marked at the onset of the conjunctivitis and were in the author's opinion sufficiently marked to be used as an aid to diagnosis. The muco-purulent discharge was generally thin, greyish, but there were also cases in which it was purulent, even very thick. On microscopical examination the conjunctival discharge showed leucocytes, and stained specimens were negative in all cases except one in which a few gram-negative cocci were discovered. Gonococcal cultures also yielded no growth. It is to be regretted that no differential leucocyte count was made. In only one case was an eosinophil count carried out: eosinophils amounted to 46 per cent, the other cells being chiefly neutrophils. The duration of the conjunctivitis varied from a few days to seven months. However, in most cases the conjunctivitis disappeared in one to four weeks (*Cf.* p. 77).

In the cases of keratitis there were both superficial and deep infiltrates, varying from round shapes, 1—2 mm. in diameter, to large pleomorphic figures. Besides such small infiltrates there appeared in one case a long and narrow bow-shaped ulcer in the cornea. The duration of keratitis varied from one to four months (*Cf.* p. 77).

The symptoms of iritis were conjunctival and pericorneal redness and discoloration of the iris. Slight precipitation was only

seldom noted in the anterior chamber, but there was a strong tendency to form posterior adhesions and therefore iris pigment was often found on the surface of the lens. Once there was blood in the anterior chamber. The duration of iritis varied from one to five months (Cf. p. 77).

UROGENITAL INVOLVEMENT

In each case the urine was tested for sugar and albumin. The former test was always negative. In a total of nine cases albumin was found (Cf. p. 56, nephropathies). Besides these investigations the urine obtained with catheter was examined in 40 cases. In 305 cases the urethral meatus and the adjacent parts were carefully washed with water and soap and immediately after this the patient passed most of the urine from the bladder, the last part into a sterilized dish. These tests were carried out once or several times (maximum 5) at weekly intervals. All urine specimens were free from albumin and sugar; the reaction was generally acid, the *pH* being in about one-half of the cases 5.5, in one-fourth 5, in one-fifth 6, and in about one-tenth the range of the *pH* was from 6.5 to 7. In five cases an alkaline urine reaction (litmus) was occasionally obtained. The microscopical examination revealed nothing pathological in the sediment. Stained specimens of catheter urine were negative for bacteria. Cultures of the catheter urine specimens from 30 patients once or several times were negative in 29 cases and one yielded *S. paratyphi B.* (Cf. p. 98). The other urine specimens were also generally negative to the Gram stain. In only six cases were found the non-pathogenic bacteria which are usually present in the urethra (so-called epithelial bacteria). In 169 cases the urinary sediment was stained for tubercle bacilli with negative result.

Diseases of the urogenital system were noted in 265 cases which corresponds to 79.3 per cent of the whole series. Table 8 gives a detailed analysis of the number and nature of these diseases.

TABLE 8

UROGENITAL INVOLVEMENT

Urethritis alone		103 cases
combined with:		
Macular eczema on the penis	63 cases	
" " and suppuration on the penis ..	6 "	
" " ulcerations " " " "	5 "	
Ulcerations on the penis	3 "	
Margins of meatus and adjacent parts reddened	24 "	
Dysuria	12 "	
Hæmaturia	4 "	
Nephropathy	9 "	
Involvement of testes or epididymis	9 "	135 cases
	Total	238 cases
		(= 89.8 %)
No clinically recognizable urethritis; other symptoms as follows:		
Macular eczema on the penis	9 cases	
" " and suppuration on the penis ..	1 "	
Dysuria	14 "	
Pain in testes	2 "	
" " penis	1 "	27 cases
	Total	265 cases
		(= 79.3 %)

URETHRITIS

Urethritis occurred in 238 cases, or 71 per cent, and in 89.8 per cent of all cases of urogenital involvement. Its subjective symptoms were usually urethral itching and burning which increased during and after urination; occasionally increased frequency was also observed. The discharge was not generally so abundant as in gonorrhœal urethritis, but occurred chiefly on pressure of the urethra. In most cases it was thin and greyish, more rarely thick and purulent. On microscopical examination the discharge showed numerous leucocytes but no bacteria, or only such as are commonly present in the urethra. Cultures were negative for gonococci (Cf. p. 99). Unfortunately no differential leucocyte count was made from the urethral pus or the mucopurulent ocular discharge. An eosinophil cell count was made from a urethral speci-

men once in each of 25 cases. The result was as follows: in 12 cases 0 per cent, in four cases 1—4 per cent, in four cases 6—10 per cent, and in five patients 17—57 per cent. The other cells were chiefly neutrophils. — The degree of smarting varied greatly from case to case. Sometimes it was very severe and caused much discomfort, sometimes it was very mild, or even entirely absent; in that case the patient only observed the urethral discharge, or even that escaped his notice and it was noted only on examination. In 24 cases the margins of the urethral meatus and the adjacent parts were reddened, occasionally pouting of the swollen urethral mucosa was observed. The duration of the urethritis varied greatly, as did the intensity of its symptoms. In some cases it seemed to clear in one day, in others it lasted for several months. The great majority (87 per cent) of the cases recovered in one to four weeks, about one-half of the cases as early as during the first week (Cf. p. 77). In all prolonged cases a marked undulation was observed in the severity of the symptoms.

CYSTITIS

Symptoms from the bladder were present in 22 cases; in 10 of these urethritis could not be clinically recognized. The diagnosis of cystitis was based chiefly on the clinical symptoms: frequency of urination amounting to 30—50 times daily, pain and tenderness on pressure in the floor of the pelvis. We had no opportunity of performing cystoscopic examinations while these symptoms were still present. Only later — when the clinical bladder symptoms had already vanished — 17 patients were submitted to cystoscopy by the urologist (Aulis Korhonen, M.D.). Some of these patients had had bladder symptoms, but some only urethritis and penile erosions. It was noted that in nine patients the region of the *trigonum vesicæ* was more or less reddened, the mucous membrane of the bladder appearing normal elsewhere. In eight patients the cystoscopic findings were quite normal. In each of the 17 cases a urine specimen was taken from the bladder in connection with cystoscopy. All specimens were clear and free from albumin. The sediment showed very few leucocytes. Stains (Löffler and Gram) and cultures (Conradi-Drigalski's agar and

blood agar) were negative for bacteria (Cf. p. 99). — In one patient who had very severe bladder symptoms but was not cystoscoped the initial and last part of the spontaneously passed urine was turbid and contained a great number of greyish lumps and floccules which did not disappear on boiling or adding nitric acid and resembled an amorphous mass under the microscope. The sediment also showed numerous leucocytes and varying numbers of erythrocytes, but no casts. In one case there was gross terminal hæmaturia, and the urine later contained visible blood floccules for some days. Stains, cultures, and dark field examinations were negative. Mild bladder symptoms were accompanied by a hæmaturia lasting for one to three days in three other cases; no casts were found and the urine was sterile. The duration of the bladder symptoms generally varied from a few days to two or three weeks. However, in one instance they occurred at irregular intervals over a period of five months, and in the case described above over nine months (Cf. p. 78).

NEPHROPATHIES

In six cases some albuminuria was noted, the 1—3 specimens obtained at intervals of two to six days being slightly positive (boiling test). In one case the amount of albumin was $\frac{3}{4}$ per mille (Esbach). These reactions later became negative. The sediment showed an increased leucocyte count, either alone or together with erythrocytes, epithelial cells, and a few hyaline and granular casts. The urine was sterile, acid. The blood pressure was normal.

In the case described above with severe bladder symptoms albuminuria appeared two months after these symptoms and lasted for nearly two months; the highest amount of albumin was 3.4 per mille.

The daily output of urine varied from 1,040 to 2,900 c.c., being generally below 2,000 c.c. The specific gravity measured 1.007—1.015. The urinary sediment now showed a large number of leucocytes, but little or no erythrocytes, except in two tests in which the latter were numerous. There were no casts. Stains and cultures were negative for any pathogenic organisms. The patient had no headache and no noticeable œdemas. The

pulse was even and regular, rate about 60 to 80 per minute. In repeated measurements the blood pressure was normal or subnormal (100/50 mm. Hg). Auscultation, X-ray, and electrocardiographic examination of the heart revealed no pathology. The number of white blood cells, which had earlier been 7,000, rose to 13,700 when nephropathy set in, and the differential count showed a "shift to the left" and monocytosis. The sedimentation rate of the blood which had fallen to 26 mm. from 53 mm. at the onset of the disease, rose again to 73 mm. The total blood cholesterol was 190 mg per cent, the blood potassium 20.9 mg per cent, and the calcium 10.3 mg per cent. Vitamin studies gave the following results. In the blood: vitamin C 0.85 mg per cent, vitamin A 112 I.U./100 c.c., carotene 22.0 γ per cent, nicotinic acid 1.20 mg per cent. In the urine: vitamin B₁ 112.7 γ /24-hour urine. Henry's and Takata's tests were negative. The patient had no fever, except for a few slight elevations of temperature.

In another case nephritis developed in addition to bladder symptoms and articular swelling. The case is reported below:

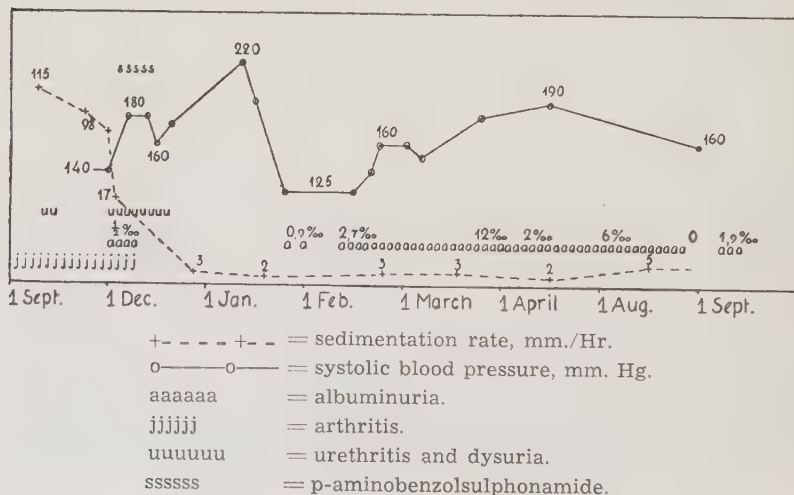
A private, aged 29. Family history non-contributory. As a child the patient had had some kind of inflammation of the eye, but he did not know the exact nature of the disease. On some occasion earlier he had been troubled by slight diarrhoea, and now for two years occasionally by dyspepsia. In 1943 he had suffered from low back pain. Urination was not painful at that time.

On August 24, 1944, while at the front, he contracted a mild dysentery which lasted for seven days. Symptoms of fever were present for two days and bloody diarrhoea for three days. Table 9 shows the patient's symptoms and their duration. Besides the urethritis and cystitis a sharply marginated erythematous skin lesion appeared around the urethral meatus, on the glans and the prepuce. Hypospadias was noted; the opening of the urethra was in the region of the frenulum. September 20. Cystoscopy (Aulis Korhonen, M.D.): The capacity of the bladder was 300 c.c. There was a fairly marked redness in the area of the trigonum and also around the ureteral orifices, especially the left. Elsewhere the mucous membrane appeared normal, erosions or ulceration were not observed. From both ureters an ordinary urinary stream escaped at regular intervals. A urine specimen obtained from the bladder on the same occasion showed no pathological findings and culture yielded no growth. Also on November 18 the urine specimen from the bladder was clear, free from albumin, cells, and bacteria. On December 2, 1944, the patient felt a pain in the sacral area and urgency of urination. He had to empty his bladder more than ten times during the night. A urine specimen obtained by catheter was yellow, rather turbid and alkaline, with an albumin content of 0.5 per mille. Numerous red blood cells, a few epithelial cells, but no casts, were

found in the sediment. The stain revealed gram-positive diplococci and consequently the patient was given p-aminobenzolsulphonamide 1 g. x 4 daily from December 2 to December 14. On December 13 the albumin, bacteria, and red cells had disappeared from the urine. There were still some residual white cells. On December 18 the patient suffered from headache and pain in the back in the area of the kidneys. The blood pressure, which had been normal at the onset of the cystitis, rose one week later to 180 mm. and remained there. On January 11, 1945, low back pain reappeared; it was accompanied by headache and slight nausea. On the next day there was gross and microscopic evidence of hæmaturia. Some white cells and epithelial cells were also found in the sediment, but there were no bacteria. The amount of albumen is seen in Table 9; the output of urine was generally equivalent to the amount of fluid taken. There were generally no casts in the urine with the exception of a few hyaline and blood casts noted on rare occasions. No œdemas were recognized. The heart was normal on clinical, röntgenological, and electrocardiographic examination. The blood count at first showed a slight degree of hypochromic anæmia and leucocytosis, but these changes rapidly disappeared. The blood non-protein nitrogen was tested four times and proved normal. The Wassermann and Kahn reactions, the gono-reaction and the serum agglutination tests for typhoid, paratyphoid, typhus, and dysentery were all negative. A specimen obtained from the pharynx did not grow hæmolytic streptococci.

TABLE 9

ONSET AND DURATION OF SYMPTOMS IN A CASE OF NEPHRITIS



A mild and temporary albuminuria present in the six cases reported above might be interpreted as a symptomatic nephrosis accompanying infectious diseases. Four of these patients also had fever — 38.1 to 38.8°C. — at the same time, but two had a normal temperature.

There was also one case in which the albumin in the urine amounted to 3/4 per mille. The sediment contained leucocytes and erythrocytes, a few epithelial cells, and hyaline and granular casts. As there was also burning on urination, urethral discharge, and tenderness to percussion in the area of the right kidney, the assumption appears justified that the urethritis had been complicated by a renal disease resembling pyelonephritis and due to the same cause as the urethritis. In another case the picture also resembled pyelonephritis (Cf. p. 56); two months after the onset of urethritis and cystitis a renal disease was superadded and lasted about two months.

The ætiology of the case of nephritis reported on p. 57 seems more complicated than that of the nephropathies described above; at the onset of the renal symptoms gram-positive diplococci were found in the urine. Some circumstances indicate, however, that in this case also the renal disease might have the same ætiology as Reiter's disease, and that the bacteriological finding would be of no ætiological importance. First, a cystoscopic examination before the renal symptoms had started revealed marked signs of inflammation in the bladder; on the same occasion the urine was free from organisms. Consequently, some factor other than the diplococcus seems responsible for the urinary tract becoming involved. Second, the diplococci disappeared from the urine after sulphonamide therapy and were not observed later, but the patient had the same rise of temperature during that therapy and afterwards. The renal symptoms occurred only intermittently during the first 2 ½ months, and it is thus uncertain whether even their first disappearance can be ascribed to the sulphonamide treatment, or whether it was spontaneous as were the later ones. The patient's articular symptoms did not at this time any longer account for the fever. On the other hand, a coincidence was observed a few times between the increase of the pathological

findings in the urine and the rise in temperature. Thirdly, it is possible that the nephritis might have been caused by the p-aminobenzolsulphonamide (total dose 52 g.), but the fact that pyelonephritis was noted already before administration of this drug is in opposition to this hypothesis.

It thus appears that nephropathies resembling symptomatic nephroses, pyelonephritis, and nephritis may also occur as symptoms of Reiter's disease.

PENILE SKIN LESIONS

Apart from a reddening of the urethral orifice and adjacent parts the series includes 87 cases with penile eruptions (equalling 32.9 per cent of the cases with urinary involvement and 26.1 per cent of the total number of cases). Ten of these patients had showed no symptoms or signs of urethritis, but the rest had had urethritis. The dermal lesion appeared most frequently and was marked in the region of the frenulum and around the urethral meatus, but also elsewhere on the glans and the prepuce. It consisted of reddish or greyish patches, 2 to 3 mm. — more rarely 5 to 10 mm. — in diameter which were sharply margined, raised from their base, and round or oval in shape. Occasionally there was a pit in the middle of the patch and the border was raised. Sometimes the lesions were coalescent and serpiginous figures thus developed. In most cases the lesions were dry and covered in places by a thin yellow brown crust; occasionally they also suppurated or there were superficial ulcerations which were, however, presumably due to secondary infection probably partly accounted for by poor penile hygiene.

This skin eruption caused the patient no appreciable discomfort and often it was noticed only by chance. It gradually disappeared, the duration varying from one week to seven months (Cf. p. 78).

Penile lesions were more frequently observed in this series than in earlier reports. They are generally not mentioned in those dealing with more extensive material, but in smaller series a few cases with penile lesions are described. However, in recent investigations where the cases have been more closely observed

such lesions have been more frequent (*Cf.* p. 23). This difference may be partly due to the fact that a skin lesion of this kind often appears later than the urethritis and is thus easily overlooked. Penile lesions seem to occur also in the absence of urethritis and thus they should be regarded as a symptom of Reiter's disease and not as a consequence of it.

INVOLVEMENT OF TESTES AND EPIDIDYMIS

Pain and tenderness in one or both testes without noticeable swelling or changes in consistency occurred in only six patients of the whole series; in two of these it was the only symptom in the urogenital system. The pain and tenderness lasted for a few days in all except one case which had a duration of four weeks. In addition to these six patients there were three who developed a unilateral orchitis and epididymitis resulting in swelling and hardening, one with a bilateral epididymitis, and one with a unilateral orchitis. Three of the patients just mentioned had initially suffered from urethral discharge or the passing of urine had been difficult. Simultaneously with the pain on urination, or after it had disappeared, pain and tenderness in the sex glands set in and they became swollen. In one patient bilateral epididymitis developed as late as 22 months after the urinary symptoms. In the cases of orchitis the testis was enlarged throughout, definitely firmer than usual, but not particularly hard, and showed a fairly marked pressure tenderness. The epididymis, on the other hand, was only once enlarged throughout; it was of the thickness of a thumb, hard and tender. In the other cases the process appeared localized rather to the caput of the epididymis, and once the cauda seemed to be involved in addition. The nodes present in these cases were about the size of a finger tip, initially hard and tender, later soft and only slightly tender. The duration of the symptoms of orchitis varied from one week to two months, but those of epididymitis lasted longer. In three cases there were still distinctly recognizable, but no longer tender nodes in the cauda of the epididymis when the patients were discharged after being treated for three, four, and five months respectively. In

one case one epididymis became asymptomatic in four, the other in nine months (Cf. p. 78).

PLEURISY

Dry and circumscribed pleurisy was definitely diagnosed in 26 cases (= 7.8 per cent). This diagnosis seemed very probable in 48 other patients. Thus with reasonable certainty the disease involved the pleura in 74 cases (= 22.2 per cent). The pleurisy was unilateral in 60 cases and bilateral in 14.

All cases of pleurisy were very mild in character and showed but few subjective and objective changes. Exudation was noted in none of the cases. In 23 instances the diagnosis was based on fluoroscopic changes which had appeared during the course of treatment. Besides these changes about one-half of the cases experienced a stitch or pain in the side when breathing or showed auscultatory changes (pleural friction), or both. In three cases no changes were observed on fluoroscopy which was carried out once, but in each of them there were subjective complaints and decidedly positive findings on auscultation.

Röntgenological examination of the chest was made in 321 cases, altogether 718 times, and changes of the pleura were noted in a total of 86 patients. In 23 of these cases active changes were observed and in 63 one or both pleural sinuses were adherent. As only 15 of the latter group had reported a previous pleurisy or pneumonia, it appears more than probable that at least in some of these patients, perhaps even 48, the pleurisy may have been caused by Reiter's disease. X-ray examination did not, however, reveal this definitely, as — contrary to the 23 cases mentioned above — no active changes in the pleura could be demonstrated. True, 38 of these cases were subjected to fluoroscopic examination only once, but 19 patients twice and 6 three times. That the pleuritis was active is, however, supported by the fact that of the 48 patients 13 showed also other subjective or objective signs: seven had a stitch in the chest or pain in the back, three pericarditis, and three auscultatory changes suggestive of pleuritis.

The series differs from those of others in that the incidence of

pleuritis was higher and there were no exudative forms. It appears that, to recognize pleuritis in connection with Reiter's disease, repeated roentgenological examination as well as frequent — preferably daily — auscultation is of great importance.

CARDITIS

The chief measures used for demonstrating heart complications were auscultation, and electrocardiographic and roentgenological examination. The shortage of films due to war conditions necessitated a reduction of the number of electrocardiographic examinations and prevented the use of the chest lead. For the same reason roentgenograms could be made in only part of the cases.

Auscultation of the heart was frequent, in most cases daily, especially during the period of fever. This chiefly aided the study of the variations in the quality and intensity of the heart sounds, and of murmurs and pericardial friction sounds. Electrocardiographic examination was made on 308 patients, the number of electrocardiograms was 837. The number of patients submitted to X-ray examination was 321, the roentgenograms numbering 253 and the fluoroscopic examinations 466. These revealed permanent pathological changes of the heart in four patients; however, on the basis of the history and the clinical course they seemed to be due to myocardial disease caused by previous myocarditis. In 23 patients the findings justified the diagnosis of carditis.

These 23 cases comprised four showing symptoms of both myocarditis and pericarditis, 16 of only myocarditis and three of only pericarditis. On the other hand, involvement of the endocardium could not be definitely demonstrated in any.

There were electrocardiographic alterations in 20 cases. The electrocardiograms of one of these patients have unfortunately been lost; in the others the following changes were observed:

In nine cases the PQ-interval was prolonged; it was either normal at first and later prolonged, or prolonged in the first electrocardiogram, becoming later normal. The PQ-interval was

considered prolonged when it was 0.21 or more; the maximum was 0.38 second. Besides a prolongation of the PQ-interval other abnormalities were observed in all nine cases, for instance widening of the QRS-complex (0.11—0.12 sec.), elevation of the ST-segments, and changes of the T-waves, or combinations of these alterations (a positive T-wave became very low or isoelectric, biphasic, or negative in Leads 1 and 2 in all three leads). It should be added that the PQ-distance was not reduced in exercise tests of two cases, on the contrary it was slightly prolonged, and there was fusion of the P- and T-waves.

In nine cases the PQ-interval was normal but pathological changes were observed in the T-wave: it became isoelectric, biphasic, or negative. These changes occurred in six patients in all three leads, in two in Leads 2 and 3, and in one case only in Lead 3. Even the last of these cases can be regarded as carditis, as besides the variations in T_3 — it was twice biphasic and once negative — a widening of the QRS-complex was noted in Lead 2 (0.11 sec.) and in Lead 3 (0.13 sec.), and a slightly elevated ST-segment in Lead 2 and 3. A pericardial rub was heard at the same time. This group of nine patients included four who showed — besides the abnormal T-wave — widening of the QRS-complex (0.11—0.13 sec.) during the course of the disease, elevation of the ST-segment, or both.

In one case the PQ-interval and the T-wave were normal, but the QRS_1 and QRS_3 were widened (0.11 and 0.13 sec.), and the ST-segment was elevated in Leads 1 and 2; ventricular extrasystoles also occurred. Further, in one case the diagnosis of myocarditis was based on electrocardiographic alterations and auscultation, but the electrocardiograms have been lost.

The diagnosis of pericarditis was, in seven cases in which it appeared certain, based on auscultatory and electrocardiographic findings. In three cases there was a pericardial friction sound; in two of these also elevation of the ST-segment in Leads 2 and 3 and in one only in Lead 1. In four other cases the ST-segment was normal, but a pericardial rub was audible in each case. The seven cases of pericarditis included three in which involvement of the myocardium could not be demonstrated, but in the rest

myocardial affection was diagnosed, as described earlier. In addition to these seven cases, the present series included six in which the diagnosis of pericarditis was probable. In four of these there was — besides myocarditis — an elevation of the ST-segment (in three patients in Leads 1 and 2, in one in Leads 2 and 3), and in two probably a pericardial friction sound; of the latter two, one had a normal electrocardiogram while the other indicated myocardial injury.

X-ray examination of the heart was made in 22 cases one to four times during the carditis, and in two cases before carditis was diagnosed. These studies revealed no pathology.

On auscultation pathological changes were found in 16 patients. Thus the heart sounds were diminished, even almost inaudible, in eight cases, and in one they were exaggerated. A pericardial rub was noted in seven cases; in three of these it was the only abnormal finding on auscultation. In three cases it was accompanied by a systolic murmur, and in one case by a diminution of the heart sounds. In two other cases, besides these seven, there was in all probability a pericardial rub and a systolic murmur at the pulmonary area. A systolic murmur was found in 11 cases in eight of which it either appeared or disappeared during the treatment. A diastolic murmur was not observed in a single case.

Slight fever occurred at times during the carditis in about half of the patients. Seven had a rise of temperature only for one to two weeks and five for a longer period, the maximum being eight weeks. The pulse rate usually corresponded to the temperature of the patient. In five cases, however, the pulse rate was rapid (c. 100 to 110 per minute), although the temperature was normal.

The sedimentation rate was generally markedly increased in the cases of carditis. It was normal in only 3 patients. As all the patients with heart involvement had also arthritis, it is difficult to judge definitely the role of either in the fever and the sedimentation rate.

There were subjective cardiac symptoms — pain in the precordium — in only four cases. In all of these a pericardial rub was also heard.

The exact time of onset and duration of the carditis is not distinctly revealed by the material, as more frequent electrocardiographic examinations could not be made (Cf. p. 63). However, in six cases the first electrocardiogram — taken 7 to 28 days after the onset of Reiter's disease — was normal, but the next tracing — 20 to 59 days after the onset — showed pathological alterations. Yet in 14 cases there were abnormalities even in the first tracing 6 to 60 days after the disease began. In one case the pericarditis started as late as 32 months after the onset; the patient still had slight articular symptoms at that time. Accordingly, it can be said that a carditis caused by Reiter's disease may occur as early as during the first week of the disease, but may also start later, even after two or three years. On the basis of clinical and electrocardiographic observations the duration of the carditis seems to vary from 1 ½ to 5 ½ months. At the end of the treatment four patients still showed slight electrocardiographic abnormalities, but as no after-examinations were carried out, it is not possible to say whether they were permanent or not.

OTHER LESIONS

Except for penile involvement (Cf. p. 60) there were comparatively few cases of skin lesions. *Herpes labialis* occurred in five cases and in one patient herpetiform vesicles appeared at the base of the nose; urticaria occurred in two patients. Twenty-nine patients had acute rhinitis at the initial stage, but only one had epistaxis; in this respect the series differs for instance from Gounelle's cases (Cf. p. 22). The specific nature of these symptoms in Reiter's disease cannot be decided on the basis of this series, because in view of the war conditions it seems that 29 cases of rhinitis in a group of 334 individuals must be looked upon as "normal". The same applies to the epistaxis, herpes, and urticaria.

During the treatment two patients developed *rupia* on the arms, trunk, and thighs; it healed well with the ordinary treatment and seemed to be identical with the hyperkeratotic lesions described earlier (Cf. p. 24).

Stomatitis occurred in nine patients. On the palate and the mucous membrane of the lips and cheeks there were greyish or reddish erythematous patches, slightly raised from their base, and about 2 mm. to 1 cm. in diameter. In addition, macular hæmatomas were sometimes present in other parts of the oral mucosa. No deep ulcerations of the mucous membrane were observed. Only some points of the mucosa were reddened, but it seemed that the process was entirely superficial in these cases too. *Fætor ex orē* or gingivitis did not occur. No pathological changes were noted in the teeth, with the exception of caries in four patients. The mucosal lesions were tender and caused discomfort especially when eating. Their duration varied from a few days to five weeks. Considering the high incidence of different kinds of stomatitis under war time conditions, it is difficult to draw any conclusions as to the specific nature of the oral mucosal lesions. However, it seemed that they differed in clinical manifestations from other war-time cases of stomatitis, which most frequently occurred in association with gingivitis and were aphthous or ulcerating and foul-smelling.

Bilateral mastitis developed in a man of 37 three months after the onset of the syndrome and while articular manifestations were still present. The patient experienced slight pain in both mammary glands where, in the region of the areola, a round, very firm and tender formation with a nodular surface and 2 cm. in diameter, could be palpated. The *areola mammæ* over it moved freely, and on pressure a small amount of colourless clear fluid escaped from the mammilla. The inflammation gradually disappeared without any special treatment, in the course of four months. This was evidently a specific, although rare, symptom of Reiter's disease which Sick (1918) has earlier described in two cases.

No symptoms were observed in the central and peripheral nervous system in the present series which in this respect differs from some previous ones (Cf. p. 20).

As regards the abdominal organs only four patients complained of dyspeptic symptoms. Two of these had achylia and one hypochylia. Röntgenological examination of the ventricle

in these cases showed normal conditions. A test meal (c. 30 g. wheat rusks or bread, 250 g. water, withdrawn after half an hour) was given to 287 patients and the results correspond roughly to those normally obtained in Finland. In none of the cases could enlargement of the spleen or liver be demonstrated and the abdominal organs also showed no other pathological changes; thus the findings in this respect agreed with several earlier studies (*Cf.* p. 22).

The urine of 305 patients was tested once or several times (maximum 5) at weekly intervals for bilirubin, for urobilinogen, and for urobilin; the tests were negative in all except 12 cases in which the urine contained urobilin and urobilinogen. As this appeared during the fever phase — and especially in view of the small number of cases — it seems that no particular importance can be attached to this fact.

FEVER

The fever of the patients was measured in the axilla. The morning temperature was taken immediately on waking and the evening temperature at about 4 p.m. before dinner, only exceptionally later in the evening.

The incidence of fever in this series corresponds roughly with earlier results, as does the height and duration of fever (*Cf.* p. 25). Table 10 shows the highest axillary temperature in the 320 cases where no other cause of fever could be demonstrated during the period of observation.

TABLE 10
BODY TEMPERATURE

	Maximum temperature (°C., axilla)			
	— 37	37,1—38	38,1—39	39,1—40,2
No. of cases	60	118	99	43
Per cent	18.7	36.9	31	13.4

60 cases = 18.7 % 260 cases = 81.3 %

The cases with an axillary temperature of over 37°C. are considered as having fever. In the 258 febrile cases where it was possible to get the information required, the duration of fever

varied from one day to more than six months, which is shown in detail in Tables 11 and 12.

TABLE 11
DURATION OF FEVER

	Duration of fever, weeks													
	0—1	2	3	4	5	6	7	8	9	10	12	14	26	
No. of cases	135	36	28	15	10	10	9	4	6	2	1	1	1	
Per cent..	52.3	13.9	10.8											
	199 = 77 %													
	Total 258													

In Table 11 the figure under the heading "duration of fever" denotes that the fever stopped during that particular week of the disease, and Table 12 again shows how many days the fever lasted in the cases in which it stopped during the first week.

TABLE 12
DURATION OF FEVER IN THE CASES IN WHICH IT SUBSIDED DURING
THE FIRST WEEK

	Duration of fever, days						
	1	2	3	4	5	6	7
No. of cases	32	30	22	8	9	8	26
Total 135 cases							

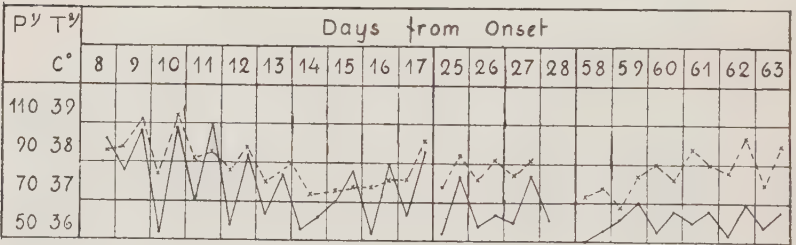
Generally the fever started gradually without actual chills; some patients, however, had a feeling of chill. No special type of fever characteristic of Reiter's disease was observed, but it was usual that the patient had no fever or was subfebrile in the morning, the temperature rising in the afternoon. The difference between the morning and evening temperature was thus generally great, even $2\frac{1}{2}^{\circ}\text{C}$. In one and the same patient the fever could be continuous and then vary indefinitely with large remissions, being even sometimes absent for days. No steep fall of temperature was observed; the fever decreased gradually, and especially in the cases in which it lasted for several weeks, there occurred at the terminal stage short, slight or marked elevations of tem-

perature of one or two days' duration at irregular intervals. In the cases where the fever lasted only one to two days it was never high. — The form of the pulse curve was roughly similar to that of the fever curve.

Definite sweating was observed in 68 patients (=20.4 per cent), but it was not very severe and occurred chiefly at the early stage of the arthritis during one or two weeks.

In Tables 13, 14, 15 and 16 some typical fever and pulse curves are given, each table showing different periods of the same patient's fever. In the diagram the morning and evening temperature are marked for each day of the disease, the days being numbered from the onset (Pulse, broken line).

TABLE 13



¹ P = Pulse rate.

² T = Temperature.

TABLE 14

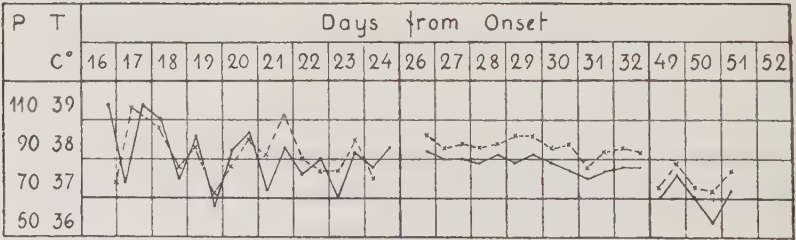
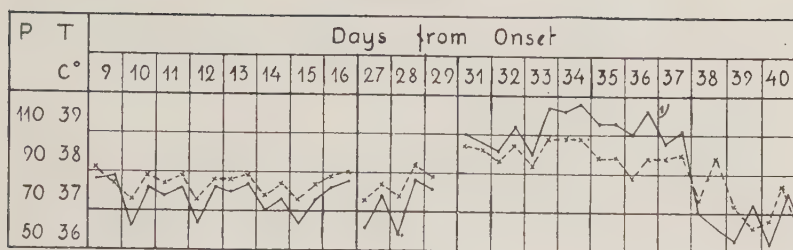
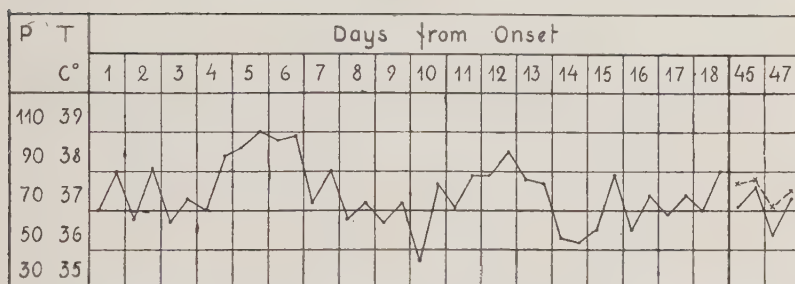


TABLE 15



¹ Pyramidon 0.6×3 daily.

TABLE 16



SEDIMENTATION RATE

The sedimentation rate in one hour was determined by the Westergren method in all the cases. The test was first made once a week and later — when the sedimentation rate was already normal — at less frequent intervals. All cases where variations in the sedimentation rate could be attributed to some cause other than Reiter's disease (*Cf.* p. 79, concurrent diseases) were omitted. Some cases, again, were omitted because the sedimentation rate was tested too seldom after the patients were allowed to have treatment at home. Among the 319 patients thus examined 26 had a normal sedimentation rate (2—10); in the others it was increased, the maximum being 11 to 50 in 103 patients, 51 to 100 in 99, and 101 to 143 mm. in one hour in 91 patients. This sedimentation rate was noted in 230 cases of 279 (82.4 per cent) dur-

ing the first month of the disease, but elevations occurred even three months after the onset. The increased sedimentation rate returned to normal in 37 patients of 200 during the first, in 140 during the second to the fourth month, and in the rest later, the maximum being 13 months.

In five cases accompanied by articular swelling or exudation in the joint cavity the sedimentation rate was normal during the whole course of the disease, and in 14 cases it was only slightly increased, between 11 and 20 mm. On the other hand, sedimentation rates up to 75 mm. were observed even in cases with only subjective articular findings. Twenty-one out of 59 such cases of arthralgia showed a normal sedimentation rate, but in the rest it was more or less increased. — At the termination of the treatment 42 patients had a sedimentation rate above 10 mm.; in 26 cases it was 11 to 15 mm., in nine 16 to 20 mm., in five 21 to 25 mm., and in one 33 mm. after barely four months' treatment, and in one instance 64 mm. as late as after more than a year. These last two patients insisted on being discharged, although their treatment was still incomplete. Except for a slight increase in the sedimentation rate — the rest of the 42 patients were either entirely asymptomatic when they were sent home, or had such mild symptoms that discharge was considered possible. These patients were requested to return if the symptoms recurred or were exacerbated. In most of the cases the sedimentation rate became normal while other symptoms were still present. Cases with swollen joints and even a large amount of exudate in the joint cavity were observed after the sedimentation rate had been normal for many months.

Of the three cardinal symptoms the articular affections seemed to cause the most marked changes in the sedimentation rate. The eye symptoms, on the other hand, were accompanied by a normal or only slightly increased sedimentation rate. However, in two cases with eye symptoms it was markedly increased (68 and 70 mm.). In the cases of orchitis and epididymitis the sedimentation was also normal or only slightly accelerated. The relation between the sedimentation rate and the heart complications has been described already (p. 65).

In a few cases of pleurisy the sedimentation rate was normal. In the majority, however, it was increased but the joints were then also affected, as in the cases of carditis.

The sedimentation rates in this series agree in the main with previous investigations (Cf. p. 26) which, however, do not mention the relation of the sedimentation rate to the different symptoms; thus a comparison on this point is impossible.

OTHER BLOOD STUDIES

The following vitamin determinations were carried out in five cases. From the blood: Vitamin A and C, carotene, and nicotinic acid. From urine: Vitamin B₁. In the same cases the blood calcium and potassium, total cholesterol and non-protein nitrogen were determined, in one instance also the blood urea. The Takata-Ara test was made in three cases and Henry's test in four. The result in all these tests were normal, except for one case, in which Henry's test was first positive, but 17 days later negative.

BLOOD PICTURE

The hæmoglobin was determined and the red and white cell count made on 302 patients repeatedly (generally 3 or 4 times, maximum 12) at intervals of one to two weeks in the initial stage of the disease and later only if the clinical findings seemed to require it. In most (3/4) of the cases the first examination was made in the second to fourth week of the disease, in less than 1/4 of the cases during the second month, and only in some instances during the first week (12 cases) or the third and fourth month (7 cases).

It was found that the hæmoglobin (Sahli) in 20 cases ranged from 52 to 60, in 70 (=23.1 per cent) from 61 to 70, and in all others (=70.3 per cent) it was higher, the maximum reaching 100. The red cell count varied as follows: in two cases from 2.9 to 3.0 mill./cu.mm., in 25 from 3.1 to 3.5 mill., in 68 from 3.6 to 4.0 mill., and in the remaining cases (=68.5 per cent) the number of red blood cells was higher, with a maximum of 5.5 mill. If a hæmoglobin of 52 to 70 (Sahli) and an erythrocyte count of 2.9 to 4

mill. are regarded as anæmia, 116 patients (38.4 per cent) were anæmic at the first examination. In 80 of the patients both the hæmoglobin and the red cell count were reduced, in 21 only the hæmoglobin, and in 15 only the number of erythrocytes. In most cases the anæmia was normochromic, including the last-mentioned 15 cases, and only a small proportion was hypochromic. In addition, a mild hyperchromic anæmia was noted in three cases, but a more detailed investigation revealed bothrioccephalus anæmia. This series does not clearly show whether the anæmia is a specific symptom of Reiter's disease. It may also be ascribed to the stress of war and the monotonous diet, but in opposition to this is the fact that most patients had had Reiter's disease for two to eight weeks before the blood count was made — there being thus time for anæmia to develop — and that anæmia was observed to set in in 12 cases during hospitalization. Accordingly, the anæmia occurring in Reiter's disease seems to be of the same type as seen in infectious diseases in general.

When these 12 cases are included it appears that anæmia was present in 128 cases, or c. 42 per cent. As previous reports have contained few statements on the red cell count and as it, according to them, has shown no pathological changes, except that Twiss and Douglas (1946) noted secondary anæmia in two cases and Storm-Mathisen (1945) in one case (Cf. p. 26), the present study should throw added light on the subject.

A study of the white blood cells revealed that the white cell count varied in 2/3 of the cases from 4,000 to 8,000. In about 1/4 of the cases it was above 8,000, ranging in 48 patients (=15.8 per cent) from 10,000 to 18,000. White cell counts under 4,000 were observed in 18 cases, the lowest figure being 3,000. A differential count showed a "shift to the left" in 64 cases (21 per cent), the percentage of neutrophil rods being 6 to 20.5. Juvenile forms were found in only two cases and then not more than 0.5 per cent. Eosinophilia (5 to 11.5 per cent) occurred in 100 patients (=33 per cent). In 41 cases (13.5 per cent) the number of monocytes was increased (10—21.5 per cent), and in 18 cases the lymphocyte count varied from 40 to 56 per cent. A thrombocyte count was made in only 13 cases; their number varied from 92,000

to 498,000. The leucocytosis seemed to be due chiefly to an increase of the neutrophil cells, and it occurred most frequently (in more than 1/2 of the cases) during the first month of disease and later more rarely. The incidence of the "shift to the left" and of monocytosis was also highest during the first month; 2/3 of the former and 3/4 of the latter cases were noted at that time. Eosinophilia was observed in 1/3 of the cases during the first, in 1/2 of the cases during the second month, and in the rest later. The blood picture in the present series agrees in the main with that described in earlier investigations (Cf. p. 26), even if it is not possible to compare the incidence of various pathological findings with previous reports as the latter lack the required data.

DURATION OF REITER'S DISEASE

a) ARTHRITIS

In all 313 cases (= 93.8 per cent) in which the arthritis was accompanied by other symptoms, the former invariably persisted after the other symptoms had vanished. Seeing that articular affections were in 43 per cent of the cases the single initial symptom of the syndrome, or a part of the initial symptom complex, and that all the cardinal symptoms in 85 per cent of the cases (Table 3, p. 44) began between the first and twentieth day of the disease, it can be said that the duration of the arthritis in this series corresponds fairly closely to that of the whole disease.

The duration is not known in 23 cases of 325, owing to the patients being transferred to other hospitals or to the clinical reports lacking definite final data. In any case the disease had lasted for some months in 20 of the patients mentioned and over one year in three patients. It is noteworthy that none of the cases with marked articular swelling recovered during the first month; the recovery began at the earliest in the second month. Of these cases 53 per cent recovered during the second to fourth month, and four patients were ill for more than one year, the longest duration being 16 months. In the cases of arthralgia, on the other hand, recovery was observed already in the second week; 24 per

cent recovered during the first month, 90.7 per cent during the first three months, the longest duration being about eight months, in one case. If all cases where the joints were involved are included, 240 cases (79.4 per cent) recovered completely; of these 205 cases (=67.7 per cent) recovered during the first five months, the incidence of recovery being highest (45 per cent) during the third and fourth months.

In addition to the cases described above resulting in complete recovery there were 62 patients (20.6 per cent) who, at the end of the period of observation, still showed a small amount of synovial exudate, slight swelling, minimal deficiency of extension or flexion, or crepitation felt on manual palpation and plainly heard at the distance of several metres. Four patients showed also marked muscular atrophy after 6, 8, 15 and 16 months' treatment. Generally these symptoms were mild and caused the patients no appreciable discomfort, except before and during bad weather.

The longest time of observation was three years; at its end the patient still had some fluid in one knee and definite crepitation in both knees. His joints moved freely and were tender only on strenuous exertion and in bad weather. After being treated at hospital and at home for 1 ½ years the patient had been doing agricultural work and during this time slow, but continuous improvement of the joint symptoms had been observed. The sedimentation rate, which was high at the onset, became normal in four months.

The greater part of the articular symptoms thus seemed to disappear in a few months, but in some cases the course was protracted and symptoms observed as late as after one to three years of treatment. Why the disease was thus protracted is not revealed in the present material. These cases had begun and were treated under similar conditions as those that recovered more rapidly. The history and examination gave no clues as to previous or concurrent diseases which might have affected the course of the illness. However, one patient whose disease had lasted 17 months and who then still showed slight articular swelling and a slightly elevated sedimentation rate, had earlier had gonorrhœal arthritis. Another patient with some fluid persisting in the knee joint but

a normal sedimentation rate after 15 months' treatment, had had an acute polyarthritis twenty years earlier. In these cases the previous joint disease may have contributed to the slow recovery, although this does not seem usually to be the case, as in 23 other cases with a previous acute arthritis a prolonged course was not observed. As regards the persistent symptoms analyzed on page 76 the presence of joint exudation definitely shows that recovery is not yet complete, although the sedimentation rate is already normal (2 to 9 mm.). The same can be said of the group with slight articular swelling. Of these cases, too, one-half had a normal sedimentation rate, and in the other half it was slightly increased (12 to 33 mm.). In the group showing crepitation only four patients had a slightly increased sedimentation rate (13 to 25 mm.), while the others (31 patients) had normal sedimentation rates. As it had appeared that the condition of the patients who were given convalescent leave had continually improved during that time, and there had even been complete recoveries, such patients were discharged at their own request after two to five months, in spite of the symptoms described above.

b) OCULAR MANIFESTATIONS

The duration of the ocular manifestations was in each case shorter than that of the arthritis. The duration of the conjunctivitis (268 cases) varied from two days to seven months; slightly less than 4/5 recovered in one to four weeks. Reddening of the conjunctivæ without other ocular changes could last for one month at a stretch, but in cases of conjunctivitis of several months' duration it was usually very mild with temporary exacerbations. Iritis (17 cases), keratitis (17 cases), and kerato-iritis (7 cases) recovered within one to five months.

c) UROGENITAL INVOLVEMENT

The affections of the urogenital system disappeared before the arthritis, as did the ocular manifestations. The duration of urethritis (202 cases) varied from one day to nine months; 87 per cent recovered in one to four weeks. It should be mentioned

further that in numerous cases (34 cases=16.8 per cent) the duration of urethritis was only one or two days and that in all cases with a longer duration (of several weeks) the severity of the symptoms undulated as in the cases of conjunctivitis. The duration of cystitis (22 cases) varied from one week to nine months, that of orchitis (10 cases) from one week to two months, and that of epididymitis (four cases) from three to nine months; the penile eczema (72 cases) lasted from one week to seven months. In three cases of epididymitis small nodes still remained when the treatment had lasted for three to five months.

As regards the duration of Reiter's disease the present series agrees fairly well with previous reports.

RECURRENCES

No follow-up studies were carried out with a view to discovering recurrences, but the army patients were notified on termination of the treatment that this disease is considered due to military service and treated at the expense of the State, and that they will receive compensation if their disability is over 10 per cent. All patients were requested to notify the hospital by letter of possible recurrences or to present themselves for follow-up examination. In view of the economic advantages it seems reasonable to believe that at least these patients, in the event of recurrences, have followed the instructions given. In cases observed for three years recurrences were noted as follows:

Recurrence of the eye manifestations was observed in a total of 50 cases, but 40 of these patients had suffered continuously from arthritis and were still being treated for it, when the eye symptoms recurred. In only 10 cases was there complete freedom from any symptoms for some time before the recurrence of the ocular symptoms. This asymptomatic interval varied from 23 days to 20 months. The interval free from eye manifestations — while arthritis persisted — varied from two days to seven months.

Urethritis recurred in six cases, in three of which no other symptoms appeared; in one case the complete triad develop-

ed with an associated epididymitis, and in one urethritis recurred three times in the course of one year. In the latter case there was a concurrent mild arthritis and, the last time the urethritis recurred, also unilateral orchitis and epididymitis. One patient developed articular swelling after the urethritis. In the cases in which only urethritis recurred there was a completely asymptomatic interval of five to 27 days, in the others one of four to 16 months. In none of these cases was recurrence of diarrhoea observed.

Recurrence of the arthritis was noted in 10 cases and in four of them it was preceded by a new diarrhoea. In five cases the arthritis recurred alone, whereas in five ocular or urogenital manifestations were superimposed. The completely asymptomatic interval varied from three to 18 months. In one case there were two recurrences after asymptomatic intervals of seven and three months. In four cases the recurrence involved only the joints (or joint) which had been affected the first time. Five patients had symptoms both in previously unaffected joints and in others, and in one case the joint originally involved remained unaffected and the symptoms were observed only in new joints.

As regards recurrences of the arthritis the series differs from Quinquand's (1874) report, according to which Reiter's disease does not tend to recur. However, recurrences of the articular, ocular and urethral manifestations have been reported several times in the recent literature, and the present series thus agrees with them (Cf. p. 32).

CONCURRENT DISEASES

In addition to the involvements described above, the patients had concurrent diseases of which some had set in prior to the dysentery and some were observed simultaneously with the first symptoms of the syndrome, while others only developed later. Thus bronchitis was noted in four cases on admission and in 14 cases later. As bronchitis, however, is very common in war time and obviously, to some extent, infectious, it seems reasonable to consider that its occurrence corresponds to the conditions at

that time and is unrelated to Reiter's disease. P n e u m o n i a was noted only once, T u b . p u l m . i n v e t . in two cases, and T u b . p u l m . s a n a t a in one instance.

Nine cases of tonsillitis occurred, but all the patients were already hospitalized or on convalescent leave at the time. There were also nine cases of hypertrophic tonsils. While at the hospital one patient contracted diphtheria and another measles. O t i t i s m e d i a a c u t a occurred in five cases, in one of which there was a concurrent sinusitis and bronchitis. G i n g i v i t i s or p a r a d e n t o s i s was noted in 14 cases, one or several carious teeth in 121 patients, and root fillings in 20. H e p a t i t i s e p i d e m i c a was diagnosed in four patients. One female patient suffered from p y e l i t i s due to mixed infection. The serum was positive for s y p h i l i s in three cases, in one of them treatment had been started before the onset of Reiter's disease. H e l m i n t h i a s i s occurred in 32 cases: one patient was infected with *Ascaris lumbricoides*, all the others with *Dibothriocephalus latus*. In view of conditions in Finland no particular significance can be attached to this incidence of helminthiasis.

A private aged 21 had had a pustular eruption on the head for half a year before the onset of dysentery; as symptoms of Reiter's syndrome appeared the eruption became worse and involved the whole body. The disease was diagnosed as *impetigo herpetiformis* and the patient later developed septicæmia in connection with which suppuration began in all joints affected by Reiter's disease. The eruption healed leaving brown areas of pigmentation but the patient died, having shown symptoms of general sepsis which was probably due to the impetigo and had found favourable conditions for spreading in the organism damaged by the syndrome. *Streptococcus hæmolyticus* grew in the aspirated pus. Autopsy confirmed the diagnosis. Because of the sepsis the autopsy material was unfortunately of no value in the study of Reiter's disease. In this connection the thought suggests itself that the cases of post-dysenteric arthritis associated with joint suppuration which have been described by earlier investigators (Cf. p. 13) may well have had a similar pathogenesis.

As regards the occurrence of concurrent diseases this series of cases correspond in the main to previous ones. However, they differ from Walther's (1940 c) in showing a considerably lower

incidence of bronchitis and angina — 5.4 and 2.7 per cent respectively, as against Walther's 13.8 and 7.4 per cent. In view of the war-time conditions, however, even Walther's figures cannot be considered abnormally high. Previous studies do not contain data on the incidence of dental caries and paradentosis in Reiter's disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

As long as no serologic or other reaction specific for Reiter's disease is known, the diagnosis must be based on the history and on other clinical data.

Whenever the typical triad develops after dysentery, diagnosis is easy. The postdysenteric cases in which there are one or two of the essential symptoms, may be looked upon as "rudimentary" forms of Reiter's disease. Diagnostic difficulties appear, however, when there has been no previous dysentery. Even then, cases with the complete triad or with two typical symptoms may be diagnosed with reasonable certainty on the basis of the clinical manifestations. But all cases showing only one of the cardinal symptoms are often difficult to differentiate from certain other diseases of the same organs. Here information regarding cases of dysentery in the immediate vicinity of the patients or a subsequent positive agglutination test for dysentery may put the examiner on the right track.

Diseases to be considered in the differential diagnosis are e.g. the Stevens-Johnson syndrome and keratosis blennorrhagica, which in some forms may strongly resemble Reiter's disease (Cf. p. 30). Differentiation may be difficult also in the case of gonorrhœal arthritis. The gono-reaction must here be regarded as a valuable aid; according to our present knowledge, it is negative in Reiter's disease. On the other hand, it should be borne in mind that the gono-reaction seems sometimes to be negative also in gonorrhœal arthritis (Klemola 1944, *etc.*). The polyarthritis in Reiter's disease differs from that due to rheumatic fever in that the symptoms of the former do not move from joint

to joint (Cf. p. 50) and that the latter generally responds well to salicylates and pyramidon. As regards the arthritides occurring as sequelæ of some infectious diseases — for instance scarlatina, typhoid, febris undulans, *etc.* — a detailed history and serological reactions are often guides to a correct diagnosis. Differential diagnosis in the case of rheumatoid arthritis may sometimes be difficult, too, for according to the literature, cases of undoubted rheumatoid arthritis may not infrequently be complicated by ocular lesions, occasionally by non-specific urethritis or a brief diarrhœa.

PROGNOSIS

On the basis of the present series the prognosis in Reiter's disease can be considered good, this agreeing with the opinion of practically all earlier observers. The prognosis for children, old people and individuals suffering from some other concurrent disease remains undecided, as such cases were extremely rare. In no case in the series of 344 patients was Reiter's disease the direct cause of death. One patient died of general sepsis obviously due to impetigo herpetiformis which had started before the onset of Reiter's disease (Cf. p. 80). As regards the anatomy and function of the joints and various organs the recovery also seemed good, although no very far-reaching conclusions can be drawn owing to the short period of observation.

TREATMENT

Importance was attached to improvement of the patient's general condition by means of good food and a varied diet as far as possible under war-time conditions. The patients were kept in bed as long as they had fever or carditis in the active stage. This rule was not so strictly adhered to as generally in cases of rheumatic fever, and most of the patients were fairly soon allowed to get up, at least to wash themselves and go to the lavatory, although inflammatory symptoms, such as slight fever, increased sedimentation rate, *etc.*, continued to be present.

In the local treatment importance was attached at first to relief of pain by temporary immobilization and aspiration together with pain-relieving medication, *e.g.* aspirin and pyramidon. To preserve or improve the function of the affected joint, daily muscular drill similar to that in the treatment of rheumatoid arthritis was used from the early stage. This therapy seemed to be extremely valuable; for instance the small joints showed a tendency to become fixed, but, when the joint was passively flexed, a snap was heard, and mobility returned immediately. Röntgen ray treatment was tried in 16 cases at the late stage of the disease. In nine of these it seemed to be beneficial, especially for the relief of pain, but it is impossible to say on the basis of these few cases whether the effect was psychological or otherwise. Altogether 100 patients were treated with ultra short waves, but objectively the recovery was not more rapid than usual, although the treatment improved the patients' sense of well-being. In the later stages hot local or whole baths were also used after which the patients felt that their joints were more supple.

In the cases of conjunctivitis zinc-cocaine-adrenaline drops were used locally and gave symptomatic relief. On the contrary, argyrol or targesin solution and noviform ointment did not seem to produce at any rate a favourable effect. The cases of iritis and keratitis were treated with atropine-noviform ointment which seemed to give subjective and objective results, and with local heat, occasionally also with sweat baths. The cases of urethritis were not treated locally but the suppurating penile lesions were washed with chloramin solution (1:1000) to cure secondary infection, and afterwards powdered with marfanil-prontalbin. Moist eczema was treated with 1—2 per cent aluminum acetate applications. Both these treatments seemed to be of benefit. When the sex glands were affected a suspensory and lead subacetate applications were initially used, and later local heat; these measures gave at least symptomatic relief.

Medication in the great majority of cases consisted of pyramidon (ad 2.4 g. daily), salicylate (ad 8.0 g. daily), and aspirin (ad 3.0 g. daily) for several weeks, but apart from relief of pain they scarcely seemed to affect the duration of the disease. In a few cases the fever decreased while swelling and exudation persisted at their earlier level. In view of the danger of spirochætosis neosalvarsan (ad 4.35 g.) was administered in four cases, and germanin and fuadin in one, although with no notable effect. Sulphonamides (seven cases) also seemed to be of no value. Injections of calcium did not lessen the conjunctival reddening or articular swelling. Gold therapy was tried on nine patients of which three stated that they felt better. On examination no difference was noted from the other patients.

Arthigon and pyrisan (*Bacillus fæcalis alcaligenes* suspension) were used for fever therapy. The former was given to 12 patients, each receiving 7 to 12 injections. Nine of them experienced relief of some kind or other, but the objective findings resembled those obtained by gold therapy. Pyrisan was given to 120 patients: in about 4/5 of the cases each patient received 12 injections, the others receiving fewer. The interval between the injections was generally three to four days and an elevation of fever to at least 39°C. was aimed at; the fever lasted for about two to four hours.

Two-thirds of the cases treated with pyrisan showed symptomatic improvement after the rise of temperature. Five cases showed also such a striking and prompt decrease, some even disappearance of the swelling of joints and sex glands immediately after the first and second pyrisan fever, as were not observed with any of the other therapeutical measures. Even with pyrisan, the results were not sufficiently pronounced to allow any definite conclusions to be drawn.

It can thus be said that none of the treatments used resulted in a prompt and general improvement.

AETIOLOGY AND PATHOGENESIS

AGE AND SEX

As stated on page 40 and in Table 1, the material is one-sided with regard to the patients' age and sex, as it is composed in the main of soldiers. However, it includes 34 women (=10 per cent), the oldest aged 55, and a boy of two years and eight months showing the typical triad (urethritis, conjunctivitis and polyarthritis).

The boy fell ill with dysentery simultaneously with the other members of the family. Early in August 1946 he had fever for two days and bloody diarrhoea. On^o August 16 he developed a bilateral conjunctivitis, a purulent urethritis was noted on August 19 and at the same time tenderness and swelling of the joints appeared (both knees and ankles and the right elbow). On September 10 blood agglutination was: typhoid neg., paratyphoid neg., Flexner (A+D+WX) pos. 1:80, and on September 20, typhoid neg., paratyphoid neg. Urine culture on September 3 was negative, and a stool culture also failed to yield any pathogenic organisms. Roentgenological examinations of the affected joints on Sept. 10 and Dec. 5 revealed no pathology. The patient showed no symptoms after less than four months.

Reiter's disease thus seems to occur both in men and in women, and even in children. In this respect the results differ from those earlier reports, according to which it is noted only in adult men (Cf. p. 11).

HISTORY

In the family history comprising the patients' parents, brothers and sisters, tuberculosis was mentioned in 65 cases, rheumatic fever or rheumatoid arthritis in 35, indefinite joint pain in 14, bronchial asthma in three, urticaria in three, crusta lactea in two

cases, and hay fever in one case. It thus appeared that no disease occupied so prominent a place in the history that it could be considered of importance in the ætiology of Reiter's disease.

Yet it should be mentioned that the series included one family of which the seven children contracted dysentery, in five cases complicated by Reiter's disease. In another family all four members contracted dysentery which was complicated in the mother, who was also pregnant, and in one of the children by Reiter's syndrome. In another case two sisters fell ill with dysentery and both developed Reiter's disease, as did also two brothers who served in the forces but in different places. These cases seem to support a familial predisposition, but their number is too small to warrant any far-reaching conclusions.

Tonsillitis occurred, or the patient complained of a sore throat in 106 cases, but in only one of them did the tonsillitis precede Reiter's disease by about one month. In seven cases the tonsillitis occurred two to five months and in 15 cases six to twelve months before symptoms of Reiter's disease appeared. In most of the cases the tonsillitis actually belonged to the earlier history. Moreover, nine patients contracted tonsillitis while symptoms of the syndrome were present or when already convalescing. The symptoms of Reiter's disease were not aggravated hereby; on the contrary, in one case complicated by septic angina they disappeared entirely during its course. For comparison the incidence of tonsillitis and of subjective throat pain was studied in the corresponding age classes in healthy subjects who had never suffered from any joint symptoms. The result showed that of 333 such individuals 239 (=71.7 per cent) had had tonsillitis or had suffered from sore throats. Accordingly tonsillitis seems to lack ætiological importance in Reiter's disease. Sixty-four patients had suffered from articular or muscular pain. In the majority of cases, however, this appeared only in cold and wet weather under front-line conditions; this seems to agree with the general incidence of articular and muscular pain at the front.

The history of the patients included no diseases, except dysentery, which might be considered ætiological factors in Reiter's disease.

CONCURRENT DISEASES

Studies regarding focal infections and other possible causative diseases revealed nothing that might be considered of consequence. If even small dental defects are considered, the series included 121 patients with one or more carious teeth and 20 with root fillings. Although in this respect no normal material has been studied, this in all probability corresponds roughly to the average dental status in Finland also in "healthy" individuals. Gingivitis or paradentosis occurred in 14 cases, hypertrophic tonsils in nine, and nodular or diffuse non-toxic goitre in 10 cases. Bronchitis was noted only in four patients on admission. Dyspepsia was very infrequent, occurring in only four cases. Test meals showed that free hydrochloric acid was absent in 66 cases and present in 221 (Cf. p. 68). *Dibothriocephalus latus* was found in 31 cases and *Ascaris* in one.

Physical examination on admission thus disclosed no diseases that might be of ætiological importance in Reiter's disease.

DYSENTERY AND REITER'S DISEASE

INCIDENCE OF DYSENTERY AND OF REITER'S DISEASE

In his series of 334 cases 322 (96.4 per cent) had had Flexner's dysentery and only 12 patients contracted Reiter's disease without a previous diarrhœa.

Isolated cases of Flexner's dysentery occurred all through the war at the front and also among the civilian population, but the disease became very extensive on the Karelian Isthmus in the summer of 1944. No other kind of dysentery was observed in Finland during the war.

According to Kokko (1945), the epidemic started about the 20th of June, 1944, spread rapidly and to an enormous extent, and practically terminated at the end of September. It seemed to be a fairly pure Flexner epidemic, as other than Flexner's dysentery bacilli were not once observed during the entire epidemic. Of 325 examined strains 3 per cent belonged to type A, 11 per

cent to type D, 6 per cent to type H, and 80 per cent to type WX (Kokko 1945).

It is impossible to state the exact number of dysentery cases, but it has been estimated that the epidemic affected approximately 150,000 individuals. Accordingly, about 0.2 per cent of them contracted Reiter's disease. In the small local Flexner epidemics in the rest of the country occurring in 1945, at least in some of them, Reiter's disease seems to have been far more frequent. The incidence of Reiter's disease in the cases with dysentery of the present series is slightly lower than that reported in the literature (Cf. p. 10). This difference is probably due to the fact that also the mild cases of dysentery, which did not apply for medical treatment, are included in this material. Such cases, according to Kokko (1945), amounted to 25 per cent of all dysentery cases.

The cases of Reiter's disease were distributed over the different months as shown in Table 17. This distribution also corresponds to the occurrence of dysentery (Kokko 1945) — the latter at an earlier period. This is seen even more clearly in the diagram (Appendix 1, p. 113).

TABLE 17

CASES OF REITER'S DISEASE CLASSIFIED ACCORDING TO THE MONTH OF ONSET

Month of onset	No. of cases
April	2
May	1
July	33
August	209
September	72
October	13
November	3
December	1
Total	334

The dysentery epidemic started on June 20, 1944, and the first patients fell ill with Reiter's disease on July 15. The curve for Reiter's disease thus begins 26 days later than the dysentery curves and also reaches a maximum somewhat later. It must also be borne in mind that the patients with Reiter's disease are

entered on the curve according to the day of onset of the syndrome, whereas the dysentery cases are classified according to the date when seen by the doctor or admitted to hospital. Of the patients with dysentery 40 per cent remained in their units for more than three days before being hospitalized (Kokko 1945). Thus the peaks in the curves for Reiter's disease and for dysentery in reality differ more than indicated by the diagram. Furthermore, the dysentery epidemic could be considered practically terminated by the end of September, but several more patients contracted Reiter's disease between October 1 and 16.

Table 18 shows the onset of Reiter's disease counted from the onset of dysentery (in 10-day periods). About 2/3 of the cases thus began 11 to 30 days after the onset of the dysentery and the longest interval was over three months.

TABLE 18

ONSET OF REITER'S DISEASE COUNTED FROM THE ONSET OF DYSENTERY

Onset, days from onset of dysentery	No. of cases
1— 10	57
11— 20	126
21— 30	74
31— 40	32
41— 50	14
51— 60	7
61— 70	3
91—100	1
Total	314

Seven of the 20 cases not included in Table 18 had had diarrhoea, but the exact date of its onset was not known. In one case the ocular symptoms had begun six days before the diarrhoea. Six patients had had no diarrhoea, but dysentery had been very common in their units. In another six cases the clinical reports mention no diarrhoea. Bloody or bloodless diarrhoea had thus been present in 322 (96.4 per cent) out of the 334 cases of the material; after or during the diarrhoea the patients had developed Reiter's disease. On the basis of clinical, sero-bacteriological, and epidemiological findings characteristic of dysentery these cases

of diarrhoea may be regarded as cases of Flexner's dysentery (Mustakallio 1944, Kokko 1945, etc.).

The time of onset is roughly similar to that reported in Dorendorf's (1917), Schittenhelm and Schlecht's (1918) and Walther's (1940 c and 1941) studies (Cf. p. 11).

As regards the place of onset it is notable that 10 out of the 11 cases of Reiter's disease in 1943 were isolated cases from various parts of our front, for instance the Karelian Isthmus, Syväri, Äänislinna, etc., and only one case occurred at a training centre. The series from 1944, on the other hand — 301 cases — was distinctly grouped round definite points of the then front line, points which correspond to the highest incidence of dysentery. Behind the lines and in the rest of the country most cases occurred along the railway lines and were the more frequent the farther east the place was situated. In the map (Appendix 2, p. 114) all cases of Reiter's disease occurring in 1944 on the Karelian Isthmus are marked by red dots; they total 224 (18 cases are excluded because only the Karelian Isthmus is given as the place where the disease set in). Each red dot thus represents one case. On the same map are marked — according to Kokko (1945) — the cases of dysentery applying for medical treatment during the ten days (August 11 to 20, 1944) when the Flexner epidemic had reached its peak on the Karelian Isthmus. Each black dot thus represents about five cases of dysentery.

Fifteen of the 21 civilian cases from 1945 are chiefly from Flexner epidemics in Helsinki and its immediate neighbourhood; the other cases, six in number, are from more distant localities.

As regards time, locality, and incidence, the occurrence of Reiter's disease thus seems to correspond to that of Flexner's dysentery. About 0.20 per cent of the patients affected with dysentery during the extensive Flexner epidemic contracted Reiter's disease. In 96.4 per cent of the cases Reiter's disease had been preceded by Flexner's dysentery. In the majority of cases (2/3) Reiter's disease set in within 11 to 30 days from the onset of the dysentery, but the former occasionally began simultaneously with the latter, or even before it. The longest interval was over three months.

THE NATURE OF THE DYSENTERY IN THE CASES COMPLICATED
BY REITER'S DISEASE

To obtain an answer to the question as to the correlation of Reiter's disease with the severity of the dysentery an attempt has been made to find a suitable standard for determining the degree of severity of dysentery. This naturally causes difficulties, as for instance the duration of the disease as a whole and the intensity of its symptoms are by no means always directly proportional. On the basis of these two criteria the dysentery preceding Reiter's syndrome has been divided into four degrees of severity as follows:

1) *Abortive dysentery:*

General condition good all the time, no symptoms of fever and practically no discomfort other than bloodless diarrhoea for one to two days.

2) *Mild dysentery:*

Slight disturbances in general condition and pain in the body, high fever for two or three days, diarrhoea for a maximum of seven days, or if rather mild, for 10 days, also blood in the stools and tenesms.

3) *Moderately severe dysentery:*

Disturbances in general condition considerably greater than in the preceding group; severe headache and pain in the body, great fatigue, circulatory collapse and dehydration phenomena may occur, diarrhoea lasting up to 15 days or, with mild symptoms, up to one month, bloody stools and tenesms.

4) *Severe dysentery:*

As above, but symptoms even more intense, patient severely dehydrated and fatigued, high fever for a long time and continued diarrhoea.

Mild dysentery was most common (181 cases), moderately severe dysentery being next in order (115). Abortive dysentery

was fairly infrequent (24 cases), and severe dysentery occurred only twice. A fairly similar proportion as regards severity prevailed in general in the Flexner epidemic on the Karelian Isthmus (Kokko 1945).

Reiter's disease thus seems to occur in all these different groups of dysentery more or less in the same proportion. Accordingly, there is no relation between Reiter's disease and the severity of the dysentery.

RELATION OF THE SEVERITY OF THE DYSENTERY TO THAT OF REITER'S DISEASE

The duration of Reiter's disease can be considered a standard of the degree of severity of the disease, since all the patients were treated under similar conditions. Judged by this criterion no definite correlation could be observed in this series between the severity of the dysentery and that of the subsequent Reiter's disease.

SERO-BACTERIOLOGICAL STUDIES OF THE ÆTIOLOGY

a) SEROLOGICAL INVESTIGATIONS

In 309 cases Wassermann and Kahn tests and also cholesterol-Wassermann tests were made on the blood. The tests were taken once, more rarely twice, the interval between the tests varying from two months to more than a year. In 306 patients these tests were negative and in three positive. The positive reactions were due to syphilis, as shown by the detailed investigations. — Thus it seems that blood tests for syphilis are not misleadingly positive in Reiter's disease.

After a few weeks or months from the onset a gonococcal complement fixation test (gono-reaction according to Kristensen) was made on 219 patients. The test was usually carried out once, in only a small number of cases twice, and in one case three times. All reactions were negative. While Kristensen (1930) states that in gonorrhœal arthritis and epididymitis there is "practically" always a positive gono-reaction after a few weeks

or months, which also agrees with clinical experience in general, the negative reaction in this material is definitely opposed to a gonorrhœal ætiology. The gono-reaction must thus be regarded as a valuable test in the differential diagnosis of Reiter's disease, especially in differentiating cases of epididymitis due to this syndrome from gonorrhœal affections of these organs.

In 191 cases serum agglutination tests were performed for typhoid, paratyphoid, and typhus fever, and in 24 cases for *Brucella abortus* Bang. The results were as follows:

Negative agglutination:

Typhoid	196 specimens
Paratyphoid	196 ,,
Typhus	193 ,,
B. abortus Bang	25 ,,

Positive agglutination:

Typhoid 1: 80	4 cases
,, 1:160	1 case
,, 1:320	1 ,,
,, 1:640	1 ,,
Paratyphoid 1: 20	1 ,,
,, 1: 40	1 ,,
,, 1: 80	4 cases
,, 1:160	1 case
Typhoid and Paratyphoid 1:320	1 ,,

Total 15 cases

In addition, the blood agglutination test was in one case positive for typhoid 1:80, negative for paratyphoid, positive for Weil-Felix 1:40, and positive for Flexner 1:64. These positive agglutinations for typhoid and paratyphoid seem to be attributable to vaccination, as all the cases concerned were soldiers who had been vaccinated against typhoid and paratyphoid several times, most recently in early spring 1944.

Agglutination tests for Flexner's dysentery were performed on 270 patients. Two different bacterial suspensions were used in the tests. In one of them only one old type of Flexner bacillus was used; it was from the Serological Department and called "Flexner II". The second suspension, on the other hand, was a mixture of three Flexner types isolated from this particular epidemic and contained equal amounts of type A, D and WX. A total of 196 blood agglutination tests were performed on 185 patients with the Flexner II suspension and a total of 132 tests on 85 patients with suspension Flexner A+D+WX. Twenty-three sera agglutinated the former suspension in titres of 1:4—1:160; 33 sera agglutinated the latter in titres of 1:20—1:40 and 61 in titres of 1:80—1:640.

Twenty-four agglutination tests for Flexner A+D+WX were performed from aspirated joint fluid. Positive agglutination was obtained in eight cases in titres of 1:20—1:320 (1:20=three, 1:40=two, 1:80=one, 1:256=one, and 1:320=one case), in the others negative.

Opinions have varied as to the height of the agglutination titre to be considered a proof of Flexner's dysentery. According to Kokko (1945), the figures stated in the literature have varied from 1:50 to 1:200. Mustakallio (1944), however, is of the opinion that in cases where agglutination is positive only for the Flexner bacillus, the height of the titre is not of very great importance. In such cases titres as low as 1:20—1:40 could be regarded as positive. On the basis of tests performed by Kokko (1945) with Flexner A+D+WX, agglutination in titres of 1:80 can be regarded as the limit which, together with the clinical symptoms, justifies the diagnosis of Flexner's dysentery. Unfortunately no control studies have been carried out in this series as regards serum agglutination, but the results have been compared with those obtained by Kokko (1945) from the same suspension in his control material; in 90 per cent the serum of healthy individuals and patients with diseases other than dysentery agglutinated the suspension in titres of 1:40 at the most. Exceptionally high agglutination values, however, were noted by him in pregnant women and in patients with skin lesions. In a

group of 378 healthy men Penttinen (1947) found agglutination titres of $\leq 1:80$ in c. 10 per cent with Flexner A+D+WX suspension.

Agglutination tests for typhoid, paratyphoid, typhus, and Flexner II were made once in each of six cases of the total 12 in which dysentery was not clinically diagnosed (Cf. p. 92); the result was negative. In one case an agglutination test was made for Flexner A+D+WX, and the serum agglutinated the suspension in titres of 1:160.

Dysentery, of course, belongs serologically to a group of infectious diseases in which fairly low agglutination titres or even frankly negative results are obtained also in cases where the clinical diagnosis is supported by a positive stool culture. In view of this, the agglutination values in this series seem to favour dysentery infection. Even the cases in which no dysentery could be demonstrated by clinical means included one where the agglutination value seems to prove the diagnosis of Flexner's dysentery. It remains to be decided, however, whether the positive agglutination reactions are due to Reiter's disease or only a proof of recent or early dysentery.

The serological tests, viz. the Wassermann and Kahn tests, gono-reaction, and agglutination tests for typhoid, paratyphoid, typhus, and B. abortus Bang were negative. On the other hand, 61 of 132 examined sera agglutinated a Flexner A+D+WX suspension in such titres (1:80—1:640) that the reaction may be regarded as confirming the diagnosis of Flexner's dysentery. Agglutination tests carried out with an old Flexner strain (Cf. p. 97) also yielded positive results in some cases.

b) BACTERIOLOGICAL INVESTIGATIONS

CULTURES

The stools of 209 patients were cultured for typhoid and paratyphoid on Conradi-Drigalski agar in a total of 279 cases, with negative results. Similar urine cultures were made in 30 cases once or several times, the specimens being obtained by catheter. One culture grew *S. paratyphi B*, the others were negative.

In this one case there was either a mixed dysentery and paratyphoid infection or a laboratory error.

Stool specimens from 209 patients were cultured for dysentery on Conradi-Drigalski* agar; the number of cultures was 290 and seven of them grew the Flexner bacillus. These seven specimens were from five different patients and yielded growth within the first to fourth week of the disease. In the case of one of these patients a stool culture was made also during the dysentery with positive result. Besides this case, stool specimens were taken only in a few cases during the dysentery. In two cases the result was positive as late as seven days before symptoms of Reiter's syndrome appeared, in the others it was either negative or for some reason or other not recorded.

The urine specimens were cultured — besides on Conradi-Drigalski agar — on a 2 per cent agar plate, and also on a 2 per cent agar plate to which had been added 5 per cent human blood. Urine cultures made in this way once or several times on 31 patients yielded no growth. Eighteen specimens of aspirated joint exudate from the knee were cultured on the same media, but failed to yield any growth.

Gonococcal cultures were made in 28 cases on McLeod medium. Swabs were obtained from the urethra in 18 cases, from the eye in nine, and from penile lesions in one case. The results were negative.

The blood was cultured in five cases in peptone water* with negative result.

In view of the fact that the hæmolytic streptococcus might be an ætiological factor in Reiter's disease, bacteriological cultures of the pharynx were made on 110 patients. The control material consisted of 107 patients treated at the same war hospital for various internal diseases. In the first group *Streptococcus hæmolyticus* (β) grew in 17 cases, whereas the result was positive

* According to investigations carried out later in the Sero-Bacteriological Laboratory, the number of cultures positive for dysentery is smaller on Conradi-Drigalski agar than on SS agar (Anttonen 1947).

* Peptone water: 40 g. peptone (Parke, Davis & Co.), 2 g. glucose, 5 g. common salt, and 1000 c.c. distilled water.

in 42 patients in the control group. It is thus evident that a hæmolytic streptococcus in the pharynx is not an ætiological factor in Reiter's disease.

Bacteriological cultures did not add to our knowledge of the ætiology of Reiter's disease.

STAINING

The urinary sediment obtained by the method described on p. 53 was studied in 305 cases, and the urine obtained with catheter in 40, either once or several times (maximum 5), at intervals of about one week with the aid of Gram's method. No pathogenic bacteria were discovered (Cf. p. 53). The same sediments were stained in 169 cases for tubercle bacilli, with negative results. Urethral specimens were stained by Gram's method in 85 cases once or several times, specimens taken from the penile lesions in six, and of the ocular discharge in 10 cases. The ocular specimens revealed no bacteria, except in one case where a few gram-negative cocci were found. The penile and the urethral specimens were either free from bacteria or contained those usually found in the urethra. Forty-four specimens of aspirated synovial exudate from the knee were also stained for bacteria, with negative result.

DARK FIELD EXAMINATIONS AND CULTURES OF SPIROCHAETE

The finding of a spirochæte in the blood of a patient described by Reiter (1916) prompted the author to carry out dark field examinations with a view to finding possible spirochætes direct from the blood or from inflammatory discharges. For this purpose specimens were taken from 10 patients at frequent intervals, especially from the blood, but also from the urine, the urethral and ocular discharge and from the aspirated synovial fluid. The examinations were carried out at various stages of the disease and of its symptoms. The blood was generally mixed with peptone water, by which method the preparations were most distinct, but heparinized, citrated, and oxalated blood was also used. The other specimens were examined

as such or mixed with peptone water or physiological salt solution. Each specimen was studied for two to six hours at a stretch by making continually new preparations, but no micro-organisms were found.

In addition, an anærobic culture* suited for spirochætal investigations was made from the blood of eight patients and the urine of one, according to Klein's (1943) method (modification of Fortner's method); this also gave a negative result.

BLOOD FILAMENTS RESEMBLING SPIROCHAETES

In the blood of all 10 patients mentioned and the urine of one, which contained also red blood cells, as well as in the blood of four healthy control persons, there were thin light threads, of the length of the diameter of one to two red cells. They were also found in several days' old peptone water cultures of the blood. They appeared to move actively with worm-like movements and resembled spirilliform organisms, but it was later found that they belonged to the "blood filaments" and hæmokoniæ known from the literature. These have occasionally been regarded as causative agents of various diseases, viz. as spirochætes. Meessen (1925), and others considered them to be the causative factors of pernicious anæmia. Yet, especially Takeuchi's (1927) studies have shown that the "blood filaments" arise from red cells by means of an unusual hæmolysis and that their movements are passive and "also probably a result of molecular movement".

As regards the origin and development of "blood filaments" the findings in this material support previous assumptions (Zeller 1923, Takeuchi 1927, *etc.*) that their origin is in the red cells, for they were found only in such specimens which contained red cells, and it was often seen that one or several "spirilla" were adherent at one end to a red cell. It thus seems that a red cell in non-physiological surroundings ruptures and from certain red cells and under certain conditions some of the contents may escape forming threads. Such a thread may separate from the

* Klein's method was modified in such a way that the plates were not fastened onto a glass tray by means of plastiline, but special plates were prepared in which the top and the bottom unite like a rabbit joint. The line of junction on the outer side was carefully covered with adhesive tape. Such plates are easier to handle and remain tight.

cell and start floating about with the currents, often strongly resembling a spirilliform micro-organism.

SKIN TESTS WITH BACTERIAL VACCINES

It is generally known that in skin tests normal persons may react positively to even very small amounts of bacterial vaccine, and, therefore, it is very difficult to discover the bacterial allergen (Kallos 1939, *etc.*). As the writer had at his disposal bacteria isolated from the Flexner epidemic concerned, it was nevertheless decided to carry out skin tests on patients with Reiter's disease and on healthy control persons. For this purpose, vaccines were prepared separately from each type of Flexner bacillus — A, D, and WX — and also from *E. coli* and *Streptococcus hæmolyticus*. These vaccines were used for *intracutaneous* injections in the following dilutions:

Flexner-type A: vaccine undiluted and in dilutions of 1:10, 1:100, and 1:1000.

Flexner-type D: vaccine undiluted and in dilutions of 1:10, 1:100, 1:1000, 1:10000, and 1:100000.

Flexner-type WX: vaccine undiluted and in dilutions of 1:10 and 1:100.

E. coli: vaccine undiluted and in dilutions of 1:10 and 1:100.

Streptococcus hæmolyticus: 200 mill. bact./1 c.c. and 2000 mill. bact./1 c.c.

0.1 c.c. of all dilutions was injected intracutaneously into the patients and the controls, who were healthy individuals on the hospital staff, including only five patients (two cases of peptic ulcer, one case of rheumatoid arthritis, one of diabetes mellitus, and one of corpus alien. pulm.). With the weak dilutions the reaction was usually small and slight, forming a red patch about 10—30 mm. in diameter, but as the concentration increased the reaction became stronger, and with the undiluted vaccines it was about 60—120 mm. in diameter and also slightly tender.

Comparing the skin reactions of the patients with Reiter's disease with those of the control series no essential differences were observed. Also, the material was too small, comprising only 29

cases and 26 controls, to allow any conclusions to be drawn. No general symptoms occurred in any of the cases and the symptoms of none of the patients with Reiter's disease were aggravated.

DISCUSSION ON THE ÆTIOLOGY AND PATHOGENESIS

As seen from above, Reiter's syndrome is not only a disease of the male; it may occur also in women and in small children. The histories of the patients and the objective findings did not disclose any other disease — with the exception of dysentery — or any other factor sufficiently marked to be considered of ætiological importance.

In the series studied a Flexner dysentery preceded Reiter's disease in 96.4 per cent of the cases. Besides, it is probable that there had been a dysentery in those cases (3.6 per cent), too, in which there was no diarrhœa, as it seems very unlikely, that persons living in the same tent or room with dysenteric patients should have escaped infection. On the other hand, the present series of cases has shown that Reiter's disease may develop after a quite mild dysentery. The assumption thus seems justifiable that the disease may appear also in cases where the patient has contracted the infection but has not had the clinical symptoms of dysentery. This opinion appears all the more justified, as we know from the investigations of Holsti (1926), *etc.*, that inflammatory processes may occur in the digestive tract even in the absence of subjective and clinically recognizable findings.

As already stated (p. 32), other diseases besides dysentery have been regarded as causative factors of Reiter's disease, *e.g.* other enteritic infections, gonorrhœal or non-specific urethritis, infections of the upper respiratory tract and of the teeth, conditions of general sepsis, furuncles. This series and experience obtained in Finland do not, however, support these assumptions, as Reiter's syndrome has not been noted in connection with these diseases although their incidence was markedly increased during the war. In particular as regards a gonorrhœal ætiology, the consistently negative results obtained in the bacteriological and serological studies do not support it.

It is natural that when the initial symptom of Reiter's syndrome is urethritis, the former is easily considered the consequence of the latter. In this series the syndrome set in with urethritis in 23.9 per cent, with joint symptoms in 23.3 per cent, with ocular symptoms in 21.9 per cent, and in the remaining cases with various combinations of these symptoms (Cf. p. 43). Hence, it appears that urethritis should not be looked upon as an ætiological disease even in the cases where it is the initial symptom, but as due to the same cause as the other symptoms of the triad.

In recent times the question of virus causation has also aroused interest (Cf. p. 35). If Reiter's syndrome, however, were a virus disease *sui generis* one would expect it to occur more often without a previous dysentery. Accordingly, it seems probable that a virus causation would only be possible in the presence of dysenteric infection.

The present material does not entirely exclude the possibility that Reiter's disease may be caused by pleuropneumonia-like organisms (Cf. p. 34). Here, however, the same applies as was stated regarding the possibility of virus causation. The spirochæte found by Reiter (1916) seems hardly to have any ætiological significance (Cf. p. 33). In addition, in his case the onset of the syndrome had been preceded by bloody diarrhœa and, consequently, dysentery as a cause cannot be ruled out.

What has been said above seems to justify the conclusion that the cases designated in the literature as post-dysenteric arthritis, Reiter's disease or syndrome, arthritis enterica, etc., are all one and the same disease and occur after dysentery infection.

The present series throws no light on the pathogenesis of Reiter's disease. It is only possible to state that a small number of patients with Flexner's dysentery (0.20 per cent) contracted Reiter's disease which, again, in the majority of cases set in at a time when different immunizing processes against the former disease are known to occur in the organism. The primary question is — why does a dysenteric infection cause Reiter's disease in so few patients? Is this due to the dysentery bacillus or to the patients themselves? The former is possible if the strains of dysentery bacilli causing Reiter's disease differ from other strains in having

a capacity for producing toxin with a tendency to injure the tissues involved in Reiter's disease. Biochemical and serological studies for the purpose of clarifying this question have not been carried out. A second hypothesis, *viz.* that the patients who contract Reiter's disease react differently to the dysenteric infection than do those who do not contract Reiter's disease, is also possible. If so, there may be a question of an altered reaction, for instance allergy or some other constitutional factor, a circumstance, which is supported by the familial disposition described on p. 89. Eosinophilia occurred in 33 per cent of the cases of this series. This may, of course, be a sign of an allergic reaction or state. As detailed biochemical and serological studies, however, as well as investigations of the allergic reaction have not been carried out it is impossible to draw any conclusions regarding the pathogenesis of Reiter's disease. On the other hand, it seems likely that its pathogenesis is similar to that of the arthritides occurring after different infectious diseases such as scarlatina, typhoid, febris undulans, *etc.* However, Reiter's disease can be distinguished even on clinical grounds from these arthritides which in most cases have a known bacterial ætiology. This may speak in favour of Reiter's syndrome being caused by the specific toxins of the dysentery bacillus.

On the basis of this series Reiter's syndrome thus seems to occur only after dysentery, and the dysentery bacillus seems to be the causative factor also in such cases in which no dysenteric infection can be demonstrated by clinical means.

SUMMARY

The present series comprises 344 cases of Reiter's disease which occurred in Finland during the years 1943—1946. The majority of the cases originated in a widespread epidemic of Flexner's dysentery on the Karelian Isthmus during the war operations in the summer of 1944. Of the patients 10 per cent were women and the youngest a boy of two years.

In about 70 per cent of the cases the complete triad (articular, ocular, and urethral manifestations) was present, about 25 per cent showed two of the essential symptoms, and 5 per cent only one of them.

Articular manifestations were observed in 325 cases (97.3 per cent), of which 316 (97.2 per cent) were polyarthritic and only nine cases (2.8 per cent) monoarthritic. The joints of the lower extremities were more frequently affected than those of the upper extremities or the vertebral column — the knee joint most frequently, and the ankle next. Besides the joints, the muscles and tendons were also sometimes involved.

Eye affections occurred in 89 per cent of the cases. They set in with conjunctivitis, iritis (22 cases) and keratitis (27 cases) appearing later. The conjunctivitis was characterized by a deep cranberry red colour and a velvety surface.

The urogenital organs were involved in 79.3 per cent, urethritis being the most common manifestation (c. 90 per cent). Cystitis occurred in 22 cases, in 10 of these unaccompanied by urethritis. Nephropathy was noted in nine patients. In six of them it appeared in the form of a mild symptomatic nephrosis, two patients developed pyelonephritis and one nephritis. Penile

lesions were present in 87 cases (26 per cent), in 10 unattended by urethritis. The testes and epididymis were affected in 11 cases, in six of them there was only testicular pain and tenderness without noticeable swelling, but in three there developed a unilateral orchitis and epididymitis leading to swelling and induration; in one a bilateral epididymitis, and in one a unilateral orchitis.

Dry circumscribed pleurisy was definitely diagnosed in 26 cases (7.8 per cent), and this diagnosis seemed very probable in 48 other cases.

Carditis was noted in 23 cases: in four there were symptoms and signs of myo- and pericarditis, in 16 only myocardial, and in three only pericardial evidence.

Less common findings were stomatitis and rupia. In one man a bilateral mastitis developed and lasted for four months.

Fever was noted in 81.3 per cent of the patients; in 13.4 per cent the axillary temperature was over 39°C. (ad 40.2°C.). The duration of the fever varied from one day (12.4 per cent) to half a year. In 77 per cent it subsided, however, during the first to third week.

The sedimentation rate was normal in 8 per cent of the cases (2 to 10 mm. in one hour) and in the others increased (ad 143 mm.). A slight secondary anæmia was observed in 42 per cent of the patients. The leucocyte count varied from 10,000 to 18,000 in 15.8 per cent of the cases, being lower in the others. A "shift to the left" was found in 21 per cent of the cases, the amount of rod neutrophils being 6 to 20.5 per cent. Eosinophilia (5—11.5 per cent) was observed in 33 per cent and monocytosis (10 to 21.5 per cent) in 13.5 per cent; in 5.9 per cent the lymphocyte count ranged from 40 to 56 per cent.

About 4/5 of the cases with arthritis became asymptomatic during the treatment which lasted from two weeks to 16 months (2/3 recovered within one to five months), and in 1/5 slight joint symptoms remained after treatment from two months to three years. The duration of the conjunctivitis varied from two days to seven months (not quite 4/5 recovered already within one to four weeks), the iritis and keratitis lasted from three

weeks to five months, the urethritis one day to nine months (87 per cent recovered in one to four weeks), the cystitis one week to nine months, the orchitis one week to two months, the epididymitis three to nine months, and the penile lesions one week to seven months. The cases of carditis recovered in three to nine months.

Recurrence of the ocular lesions occurred in 50 cases, of urethritis in six, and of arthritis in 10 cases. The asymptomatic intervals varied from five days to 20 months.

On the basis of the present series it can be stated that the prognosis in Reiter's disease is good, also as regards the anatomical and functional recovery of the various organs.

None of the treatments used, *viz.* medication (salicylates, pyramidon, aspirin, salvarsan, sulphonamides, *etc.*), fever therapy (pyrisan), and radiation (Röntgen, short waves), seemed to bring about a rapid general recovery. On the contrary, the disease seemed to have a self-limited course.

There was a previous Flexner's dysentery in 96.4 per cent of the cases, 2/3 contracting Reiter's syndrome within 11 to 30 days from the onset of the dysentery.

Blood Wassermann and Kahn reactions and the gono-reaction were negative. Serum agglutination tests for typhoid, paratyphoid, typhus, and *B. abortus* Bang gave a negative result. On the other hand, 61 out of 132 examined sera agglutinated a Flexner A+D+WX suspension in titres of 1:80—1:640.

Bacterial cultures and dark field examinations of stools, urine, blood, and inflammatory discharge were also negative. In only five cases did the stool cultures grow the Flexner bacillus.

On the basis of this material Reiter's disease seems to occur only after dysenteric infection.

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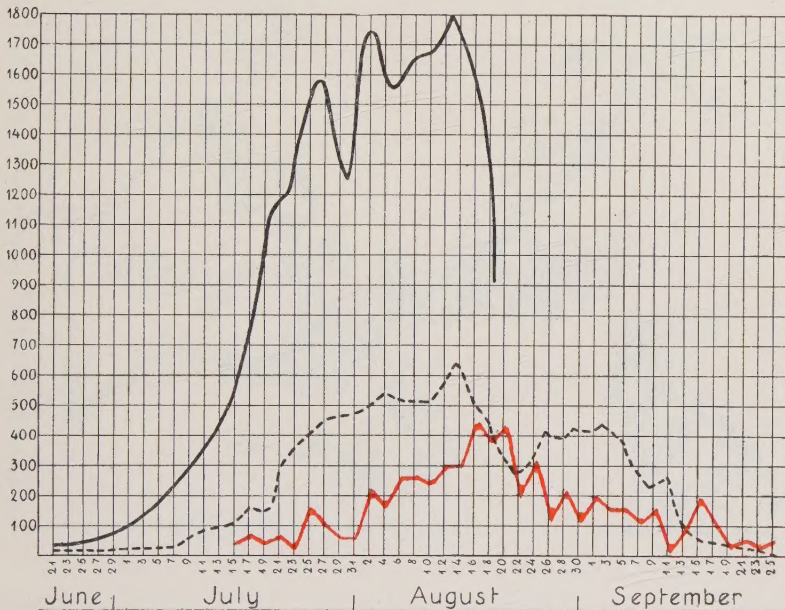
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DIAGRAM

INCIDENCE OF FLEXNER'S DYSENTERY AND REITER'S DISEASE ON THE
KARELIAN ISTHMUS IN THE SUMMER 1944.



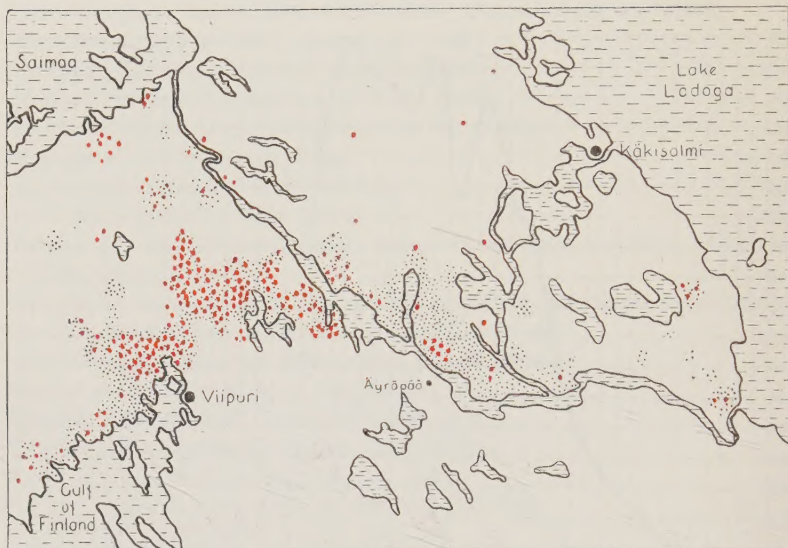
The number of all cases of diarrhoea applying for medical treatment between June 20 and August 20, 1944 (top curve), that of all hospitalized cases up to Sept. 25, 1944 (middle curve), (according to KOKKO 1945), and that of all cases of Reiter's disease up to the latter date (lowest curve).

The dates are shown in such a way that the curve for June 21 denotes the total number of cases on June 20 and 21, that for June 23 the total number of cases on June 22 and 23, and so on.

In the ordinate five cases of Reiter's disease correspond to 100 cases of dysentery.

MAP

(Kokko 1945)



The regional distribution of the cases of dysentery applying for medical treatment during 10 days (August 10—20, 1944) when the Flexner epidemic was at its peak on the Karelian Isthmus and of all cases of Reiter's disease occurring there during the whole epidemic. Each black point represents about five cases of dysentery, while each red point denotes one case of Reiter's disease.

The Russian attack launched on June 9, 1944 with superior force on the Karelian Isthmus stopped after 2 weeks and our front was stabilized in the main at the line: the west and north sides of Viipuri—Äyräpää—Vuoksi—Ladoga; the front remained there — except for small local variations — till the end of the war.

